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Applicant:
(Name and address)

Pantheco A/S
Bøge Allé 3
DK-2970 Hørsholm
Denmark

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Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

MODIFIED PNA MOLECULES

The present invention concerns novel drugs for use in combating various diseases. More particular the invention concerns peptide nucleic acid (PNA) drugs, which are optionally modified in order to obtain novel PNA molecules with cell-specific delivery.

BACKGROUND OF THE INVENTION

Antisense agents offer a novel strategy in combating diseases, as well as opportunities to employ new chemical classes in the drug design.

Oligonucleotides can interact with native DNA and RNA in several ways. One of these is duplex formation between an oligonucleotide and a single stranded nucleic acid. Another is triplex formation between an oligonucleotide and double stranded DNA to form a triplex structure.

Results from basic research have been encouraging, and antisense oligonucleotide drug formulations against viral and disease causing human genes are progressing through clinical trials. Efficient antisense inhibition of bacterial genes also has wide applications.

Peptide nucleic acids (PNA) are compounds that in certain respects are similar to oligonucleotides and their analogs and thus may mimic DNA and RNA. In PNA, the deoxyribose backbone of oligonucleotides has been replaced by a pseudo-peptide backbone (Nielsen et al. 1991 (1)). Each subunit, or monomer, has a naturally occurring or non-naturally occurring nucleobase attached to this backbone. One such backbone is constructed of repeating units of N-(2-aminoethyl)glycine linked through amide bonds. PNA hybridises with complementary nucleic acids through Watson and Crick base pairing and helix formation (Egholm et al. 1993 (2)). The Pseudo-peptide backbone provides superior hybridization properties (Egholm et al. 1993 (2)), resistance to enzymatic degradation (Demidov et al. 1994 (3)) and access to a variety of chemical modifications (Nielsen and Haaima 1997 (4), WO 94/25472, WO98/03542).

PNA binds both DNA and RNA to form PNA/DNA or PNA/RNA duplexes. The resulting PNA/DNA or PNA/RNA duplexes are bound with greater affinity than corresponding DNA/DNA or DNA/RNA duplexes as determined by the melting point temperature (Tm). This

high thermal stability might be attributed to the lack of charge repulsion due to the neutral backbone in PNA. In addition to increased affinity, PNA has also been shown to bind to DNA with increased specificity. When a PNA/DNA duplex mismatch is melted relative to the DNA/DNA duplex, there is seen an 8 °C to 20°C drop in the melting point temperature.

Furthermore, homopyrimidine PNA oligomers form extremely stable PNA_2-DNA (RNA) triplexes with sequence complementary targets in DNA or RNA oligomers. Finally, PNA's may bind to double stranded DNA or RNA by helix invasion.

An advantage of PNA compared to oligonucleotides is that the PNA polyamide backbone (having appropriate nucleobases or other side chain groups attached thereto) is not recognised by either nucleases or proteases and are thus not cleaved. As a result, PNA's are resistant to degradation by enzymes unlike nucleic acids and peptides.

For antigene and antisense application, target bound PNA can cause steric hindrance of DNA and RNA polymerases, reverse transcription, telomerase and of the ribosomes (Hanvey et al. 1992 (5), Knudsen et al. 1996 (6), Good and Nielsen 1998 (7,8)), by targeting, among others, DNA, mRNA, rRNA, or tRNA.

A general difficulty when using antisense agents is cell uptakeand targeting of specific organs. A variety of strategies to improve uptake can be envisioned and there are reports of improved uptake into eukaryotic cells using lipids (Lewis et al. 1996 (9)), encapsulation (Meyer et al. 1998 (10)) and carrier strategies (Nyce and Metzger 1997 (11), Pooga et al, 1998 (12)).

WO 99/05302 discloses a PNA conjugate consisting of PNA and the transporter peptide transportan, which peptide may be used for transport cross a lipid membrane and for delivery of the PNA into interactive contact with intracellular polynucleotides.

US-A-5 777 078 discloses a pore-forming compound, which comprises a delivery agent recognising the target cell and being linked to a pore-forming agent, such as a bacterial exotoxin. The compound is administered together with a drug such as PNA.

WO 96/11205 discloses PNA conjugates, wherein a conjugated moiety may be placed on terminal or non-terminal parts of the backbone of PNA in order to functionalise the PNA. The

conjugated moieties may be reporter enzymes or molecules, steroids, carbohydrate, terpenes, peptides, proteins, etc. It is suggested that the conjugates among other properties may possess improved transfer properties for crossing cellular membranes.

WO 98/52614 discloses a method of enhancing transport over biological membranes. According to this publication, biological active agents such as PNA may be conjugated to a transporter polymer in order to enhance the transmembrane transport. The transporter polymer consists of 6-25 subunits; at least 50% of which contain a guanidino or amidino sidechain moiety and wherein at least 6 contiguous subunits contain guanidino and/or amidino sidechains. A preferred transporter polymer is a polypeptide containing nine arginine subunits ($(Arg)_9$).

However, the present methods of transport of PNA oligomers across biological membranes lack efficiency and specificity. Only little information is available on the pharmacokinetic behaviour of PNA oligomers, e.g. the dynamic and kinetic mechanisms of exogenous absorption, biotransformation, distribution, release, transport, uptake, and elimination of PNA oligomers as a function of dosage and extent and rate of metabolic processes. However, data indicates that PNA oligomers are fairly quickly excreted in the urine according to McMahon et al (2002 (13)), being a rather hydrophilic compound, which rarely binds to proteins like albumin in serum.

It could be of significant medicinal interest to functionalise the PNAs, in order to control the bio-distribution of the molecule. Functionalisation of the PNA backbone may dramatically change the physico-chemical properties of the PNA, and it is plausible that such changes would significantly influence its pharmacokinetic behaviour.

Zhang et al (2001 (14)) describes a method by which uptake of PNA oligomers in a liver cell was promoted by modifying the terminal ends of PNA with lactose. Lactose, being recognized by the hepatic asialoglycoprotein receptor, provided an efficient entry of lactose modified PNAs into HepG2 cells.

Biessen et al (2002, (15)) presents work in which the parenchymal liver cell uptake of antisense PNA drug was improved by targeting to the asialoglycoprotein receptor of the liver cell, a glycoconjugated antisense PNA. The PNA was conjugated with N-acetyl-galactosaminyls at the 5' end through lysine side chain linkers.

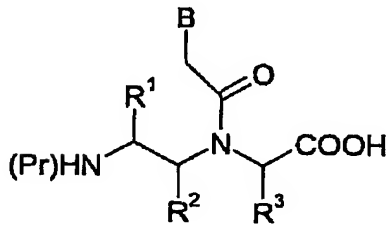
Prior art shows an increased organ and cell specificity of PNAs by end glycosylation of the PNA. However, incorporation of the saccharides into the PNA backbone would improve the medicinal chemistry opportunities, the biostability and biodistribution of the drug, resulting in lower dosage and reduced side effects.

SUMMARY OF THE INVENTION

The present invention relates to glycosylated peptide nucleic acid (PNA) monomers. More particular, the invention concerns the incorporation of glycosylated monomers into an antisense PNA oligomer, in order to improve the cell and/or organ-specific uptake of PNAs and thereby the pharmacokinetic behavior.

It has been found that by integrating saccharides within PNA monomers and by subsequent incorporation of at least one modified PNA monomer in an antisense PNA oligomer, an enhanced efficacy and organ-specificity is observed, without major influence on the DNA or RNA hybridisation potency of the PNA. The important feature of the modified PNA molecules is the incorporation of at least one glycosylated PNA monomer in the PNA oligomer chain. This results in versatility in synthesis and design in terms of character, position and number of saccharides, which is crucial for biological activity and also high bio-stability.

Thus, the present invention concerns a PNA monomer of formula (I):



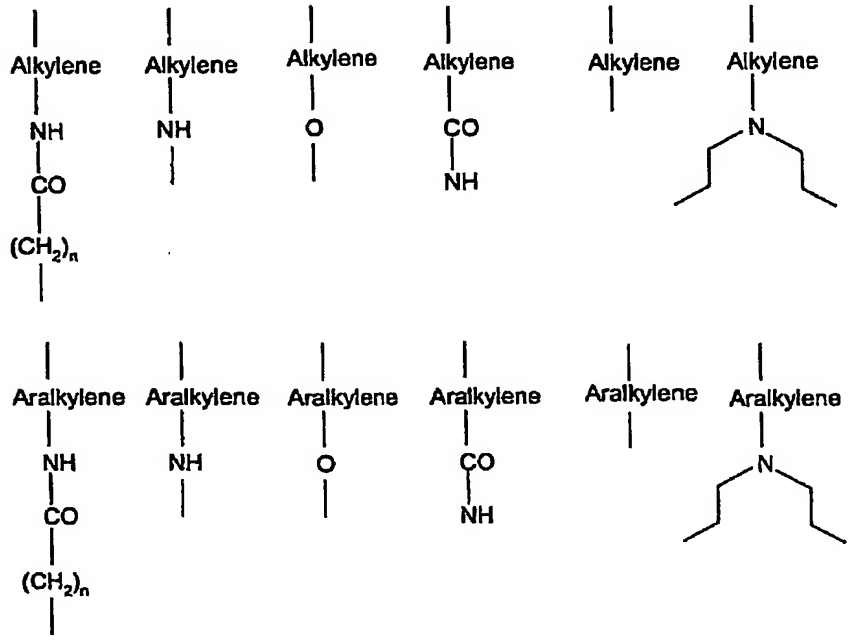
(I)

wherein B is a naturally-occurring nucleobase preferably A, T, G, or C, or a non-naturally-occurring nucleobase;

(Pr) is hydrogen or a protection group;

R^1, R^2 and R^3 are, independently, hydrogen, an amino acid side chain, or an C_{2-6}-alkyl, aryl,

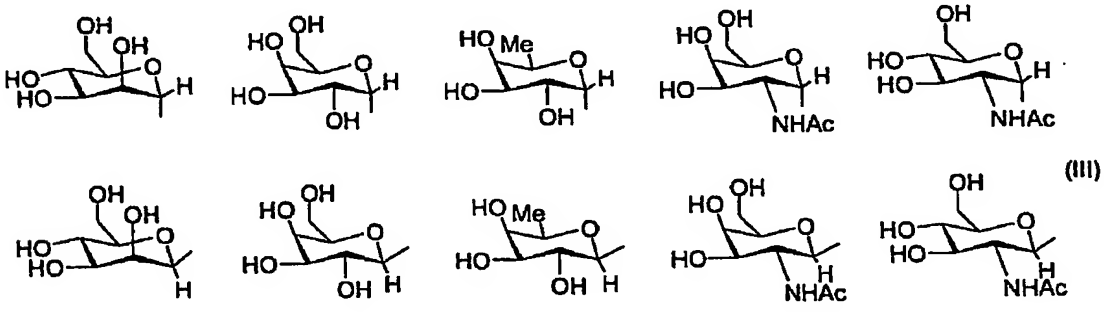
aralkyl, heteroaryl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy- or alkoxy- or alkylthio-substituted C_{1-6}-alkyl, $-NR^4R^5$, (wherein R^4 and R^5 independently are hydrogen, C_{1-6}-alkyl, hydroxy- or alkoxy- or alkylthio-substituted C_{1-6}-alkyl), or Z^1-Z^2, wherein Z^1 is a bond or one of the radicals of formula (II):



(II)

wherein n is form 0 to 8;

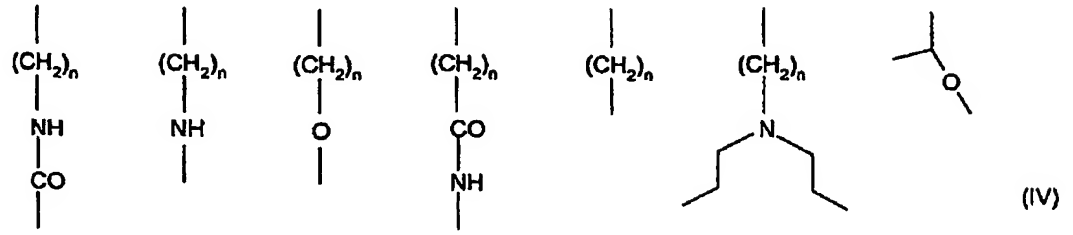
and Z^2 is alfa- or beta forms of a monosaccharide, a disaccharide, a polysaccharide, or one of the radicals of formula (III):



(III)

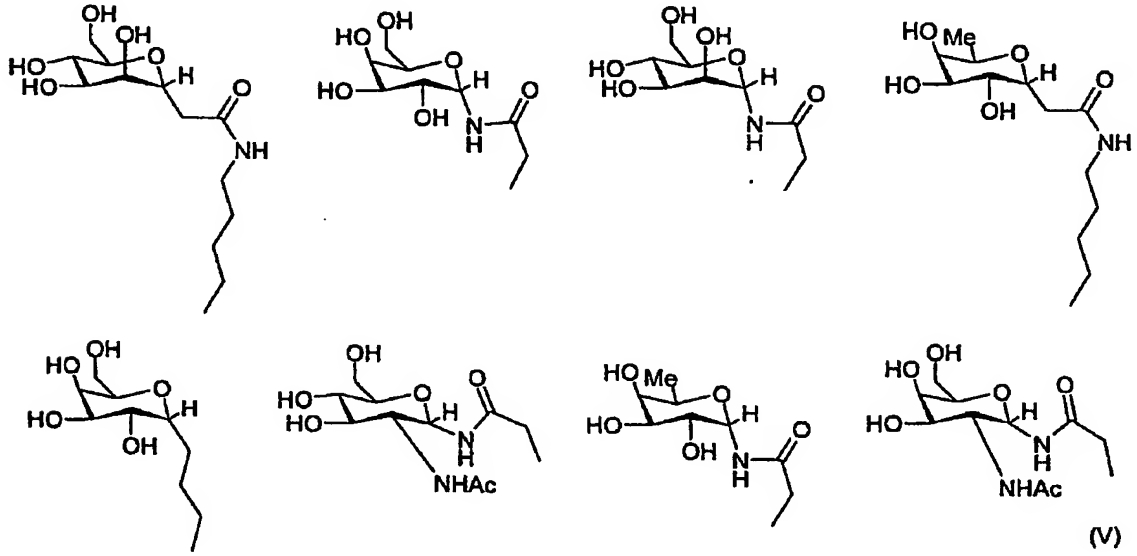
provided that at least one of R^1, R^2, or R^3 is Z^1-Z^2.

Enclosed is also a compound according to claim 1, wherein Z^1 is one of the radicals of formula (IV):



(IV)

Enclosed is further a compound according to claim 1 or 3, wherein Z^1-Z^2 comprises ligands of formula (V):



(V)

or beta-forms hereof.

Enclosed is also a peptide nucleic acid oligomer with from 4 to 50 monomers selected from the group consisting of PNA monomers and at least one monomer of claim 1, said PNA oligomer conjugated either directly or through a linking moiety to hydrogen or a reporter enzyme, a reporter molecule, a steroid, a carbohydrate, a terpene, a peptide, a protein, an aromatic lipophilic molecule, a non aromatic lipophilic molecule, a phosphorlipid, an intercalator, a cell receptor binding molecule, a crosslinking agent, a water soluble vitamin, a lipid soluble vitamin, an RNA/DNA cleaving complex, a metal chelator, a porphyrin, an alkylator, or a polymeric compound selected from polymeric amines, polymeric glycols and polyethers.

In one aspect of the invention, the modified PNA molecules are used in the manufacture of medicaments for the treatment or prevention of a disease selected from bacterial and viral infections, cardiac or vascular diseases, metabolic diseases or immunological disorders or for disinfecting non-living objects.

In a further aspect, the invention concerns a composition for treating or preventing disease selected from bacterial and viral infections, cardiac or vascular diseases, metabolic diseases or immunological disorders or for disinfecting non-living objects.

In another aspect, the invention concerns the treatment or prevention of disease selected from bacterial and viral infections, cardiac or vascular diseases, metabolic diseases or immunological disorders or for disinfecting non-living objects.

Preferred targeting is organ related diseases e.g. liver diseases such as hepatitis and liver cancer, known for a person skilled in the art.

In yet a further aspect, the present invention concerns a method of identifying specific advantageous antisense PNA sequences, which may be used in the modified PNA molecule according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

Antisense PNAs can inhibit bacterial gene expression with gene and sequence specificity (Good and Nielsen 1998a,b (12, 13) and WO 99/13893). The approach may prove practical as a tool for functional genomics and as a source for novel antimicrobial drugs. However, improvements on standard PNA are required to increase antisense potencies. The major limit to activity appears to be cellular entry and cellular specificity. Cell membranes effectively exclude the entry of large molecular weight foreign compounds, and previous results for in vitro and cellular assays seem to show that the cell barrier restricts antisense effects. Accordingly, the present invention concerns strategies to improve the activity and specifidity of antisense potencies.

Without being bound by theory, it is believed that glycosylation of PNA oligomers lead to an

improved cell specific PNA uptake. It is believed that the glycosylated peptides are recognised by receptors in cell membranes such as the hepatic asialoglycoprotein receptor thereby taken up through the glucose pathway, allowing the modified PNA molecule to cross the cell wall, reaching structures inside the cell, such as the genome, mRNA's, the ribosome, etc.

According to the invention, PNA molecules modified with saccharides enable specific and efficient inhibition of genes with nanomolar concentrations. Antisense potencies in this concentration are consistent with practical applications of the technology. It is believed that the present invention for the first time demonstrates that peptides with a certain pattern of glycosylation can be used as carriers to deliver PNAs across cell membranes. Further, the present invention has made it possible to administer PNA in an efficient concentration, which is also acceptable to the patient.

The terms "C_{1-6}-alkyl" as used herein, represent a branched or straight alkyl group having from one to six carbon atoms. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl and the like.

The number of modified PNA monomers in the PNA oligomer may be chosen between 1 and full modification. It appears that at least 2 monomers, according to claim 1, are preferable to obtain the advantageous effect.

The modified PNA molecule according to the present invention comprises a PNA oligomer of a sequence, which is complementary to at least one target nucleotide sequence in the target cell. The target may be a nucleotide sequence of any RNA, which is essential for the growth, and/or reproduction of the cell.

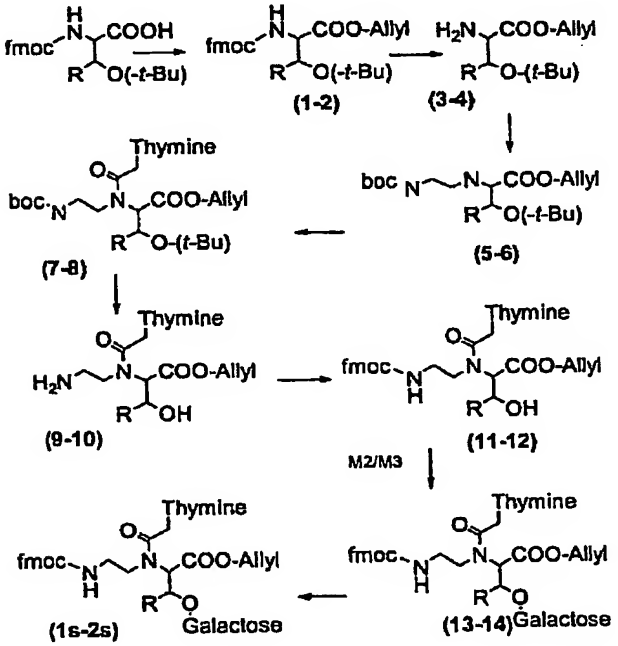
The binding of a PNA strand to a DNA or RNA strand can occur in one of two orientations, anti-parallel or parallel. As used in the present invention, the term complementary as applied to PNA does not in itself specify the orientation parallel or anti-parallel. It is significant that the most stable orientation of PNA/DNA and PNA/RNA is anti-parallel. In a preferred embodiment, PNA targeted to single strand RNA is complementary in an anti-parallel orientation.

The ability of PNAs to act as an antisense drug may be measured in many ways, which should be clear to the skilled person. To illustrate one way of preparing glycosylated PNA monomers with subsequent measuring of cell specificity, the following procedure may be used. However, the present invention is not limited hereto.

Preparation of O-glycosylated PNAs

The initially employed strategy is outlined in Scheme 1. As ortogonal protection group for the synthesis of O-glycosylated PNAs, Fmoc, *tert*-butyl and allyl were applied for amine, hydroxyl and carboxylic acid protection, respectively.

Scheme 1



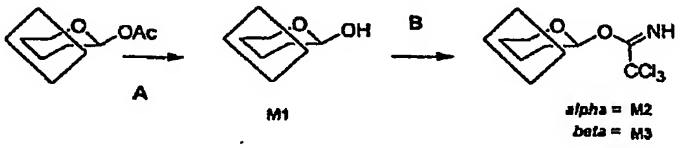
R=H) 1, 3,5,7,9,11,13,1s
R=methyl) 2,4,6,8,10,12,14,2s

Initially, the carboxyl group of Fmoc-serine(t-Bu)-OH and Fmoc-threonine(t-Bu)-OH were allylated using allyl bromide in presence of DIPEA (18) to obtain high yields of **1-2**. Fmoc-deprotection by piperidinolys treatment gave the free amine of **3-4** (19). The PNA backbone **5-6** were prepared using 2-Boc-aminoacetaldehyde (20) by reductive amination in presence of sodium cyanoborohydride. Subsequently, thymine-1-yl acetic acid (21) was condensed to the PNA backbone to give **7-8**. Boc and *tert*-butyl group removal by TFA resulted in the intermediates **9-10**. The ethereal solution was neutralised by addition of excess solid sodium

carbonate. The free amine was re-protected with Fmoc using Fmoc-O-succinimide to obtain **11-12**.

Galactose donors were prepared by the method shown in scheme 2. Commercially available β-D-galactose pentaacetate was converted stereoselectively to the 1-O-deacetylated form **M1** by treatment with ammonia in a THF-methanol solution. The reaction was monitored by TLC, in order to avoid undesired further deacetylations, and **M1** was obtained in quantitative yield in the α-form (16). Galactosyl trichloroacetimidate derivatives **M2** & **M3** were prepared by the method of Schmidt et. al. (17). *In situ* deprotonation of **M1** under basic condition (K_2CO_3), reaction with trichloroacetonitrile followed by separation on silica gel column, gave α and β anomers in good yields.

Scheme 2

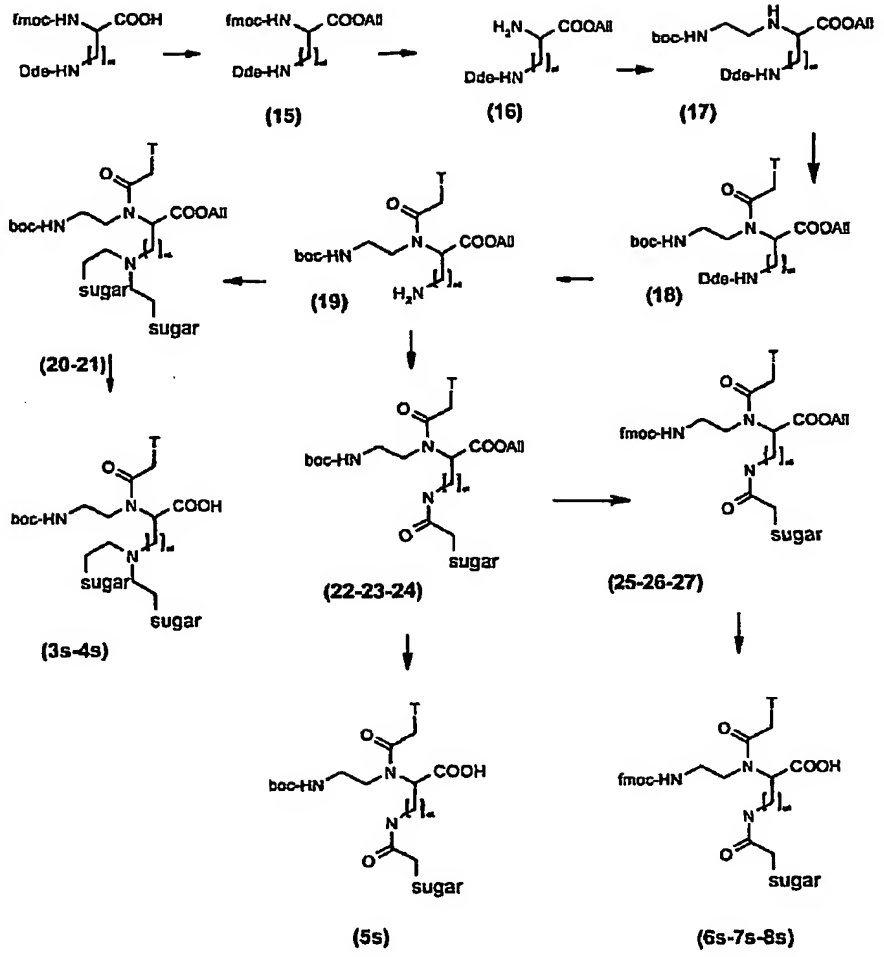


A) ammonia in THF-methanol (7:3 v/v), 1.5 h, rt, (≅ 100%).
B) K_2CO_3, CCl_3CN, mol. sieves. 4A°, DCM, over night, rt, purification by silicagel chromatography (hexane-EtOAc 2:1 v/v) → α: 36%, β: 48%

The reaction of both α- and β-galactosyl trichloroacetimidates with **11** gave **13** as a 1:1 anomeric mixture, and reaction with **12** gave **14** predominantly as the β-form. The β-glycosidic linkage in **13** and **14** were verified by the ^1H NMR triplets at δ 5.05 ppm and 5.08 ppm respectively ($J_{1,2}$ = 7.7 Hz). Finally, removal of the allyl group was performed in a high yield by treatment with N-ethyl aniline in the presence of catalytic amount of tetrakis $(Ph_3P)_4Pd$ to give **1s-2s**.

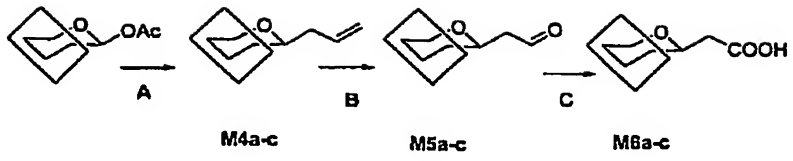
Preparation of lysine based N-C-glycosylated PNAs

Scheme 3



N-Fmoc-lysine-*N'*-(Dde)-OH was allylated using allyl bromide in presence of DIPEA and heating (18) resulting in **15**. Following Fmoc deprotection with 20% piperidine in DCM, the free amine of **16** was achieved. It has been reported that the protection group Dde is able to migrate from the side chain of lysine to an unprotected amine group of another lysine residue (22). Therefore, fresh **16** was used for the synthesis of the PNA backbone **17**. Subsequently, thymine-1-yl acetic acid (21) was condensed to the PNA backbone to yield **18**. The Dde protection group was removed by 2% hydrazine in DMF to give **19**. Allyl alcohol was added the deprotection solution to prevent reduction of the allyl group by hydrazine (23).

Scheme 4



a) galactose
b) mannose
c) fucose

A) Allyltrimethylsilane

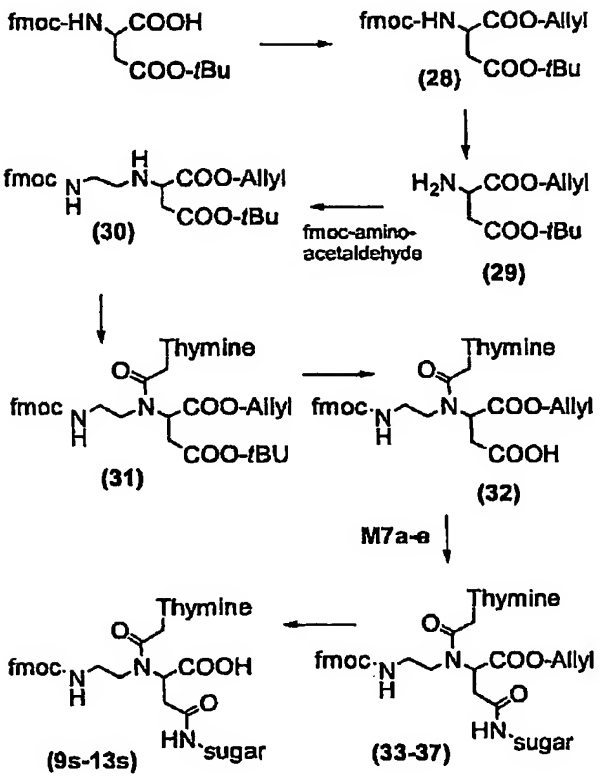
B) OsO_4, KIO_4, dioxane-water (8:2 v/v), 12h, rt, (80%).

C) 5% aqueous NaH_2PO_4, 1M aqueous $KMnO_4$, t-BuOH, 15 min, rt, (85%).

The sugar derivatives **M6** were prepared by standard literature methods (Scheme 4). Per-acetylated galactose, mannose and fucose were converted to the corresponding α-C-allyl-derivatives **M4** (24) and only α-epimers were isolated. **M4** were then oxidated to (α-D-)-acetaldehydes **M5** (25) using potassium periodate in the presence of OsO_4 as catalyst. Further oxidation of the galactose and mannose derivatives by KMnO4 gave the corresponding acids **M6** (26). Attachment of 2 eq of **M5a** or **M5c** (galactose, fucose) derivatives to the free amino group of **19**, and subsequent reduction by $NaCNBH_3$ gave good yields of **20-21**. The reaction of **M6a-c** with **19** in the presence of DCC and DhbtOH gave **22-24**. These products were converted to the Fmoc protected derivatives in two steps. They were first treated with 5% TES in TFA in order to remove the Boc group. The ethereal solution of the intermediates were neutralised with excess solid sodium carbonate, and the free amine re-protected with Fmoc using Fmoc-*O*-succinimide to obtain **25-27**. Removal of the allyl protection group from **20-22** and **25-27** yielded **3s-7s**.

Preparation of N-glycosylated PNAs

Scheme 5



N-Fmoc-L-asp(OtBu)-OH was allylated to give **28.** The fmoc group was removed and the free amine **29** reacted with fmoc-aminoacetaldehyde (27) to give **30.** Fmoc-aminoacetaldehyde was prepared by oxidation of fmoc-amino-2,3-propandiol (28) with potassium-*m*-periodate in dioxane-water (8:2 v/v). Thymine-1-ylacetic acid was attached to the backbone **30** to give **31.** tButyl group on the side chain carboxylic acid was removed with 5% TES in TFA to give **32** in a moderate yield. All glycosylamines (scheme 6) were prepared by standard literature methods (29) via glycosyl-azides (30) and were obtained as β-epimers.

Scheme 6

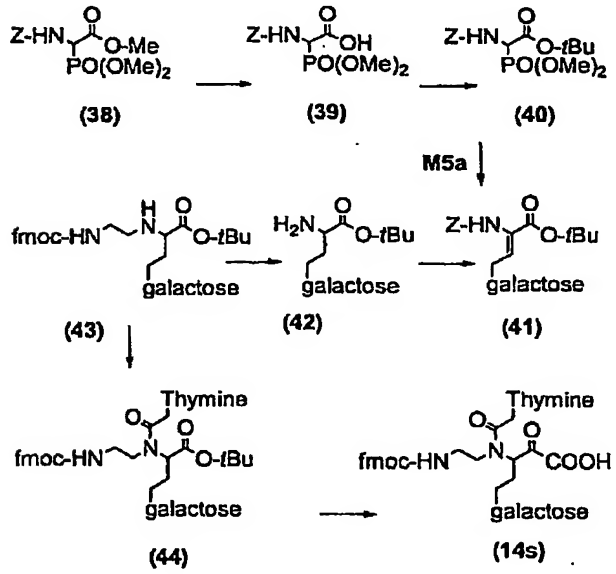
M7a-e

M7a) R=Br, R'=OAc, galactose
M7b) R=Br, R'=OAc, mannose
M7c) R=Br, R'=OAc, fucose
M7d) R=Cl, R'=NHAc, glucosamine
M7e) R=Cl, R'=NHAc, galactosamine

Attachment of these sugar-amine compounds to the free carboxyl group of **32** was accomplished by the reaction of 2 eq of amine in presence of DCC and DhbtOH to give **33-37**. Final removal of the allyl groups was performed in a high yield whereby **9s-13s** were obtained.

Preparation of C-galactosylated PNA

Scheme 7



The C-galactosylated PNA monomer was prepared from phosphonate **38** (Scheme 7). Alkaline hydrolysis of **38** in methanol afforded carboxylic acid **39**, which was subsequently converted to the t-Butyl ester **40** in 90% yield by treatment with EEDQ in t-butanol and chloroform for 24 h. Condensation of galactosyl-aldehyde derivative **M5** with phosphorylglycine t-butyl

ester **40** in the presence of *N,N,N',N'*- tetramethylguanidine as base gave **41** a mixture of E/Z isomers (5:95). As already pointed out by *U. Schmidt* and co-workers (31), the use of a strong base such as DBU or TMG favours the formation of the Z form. The E/Z ratio of **41** was measured to approximately 1:20 by proton NMR spectroscopy. Hydrogenation of **41** reduced the double bond and removed Cbz simultaneously, whereby intermediate **42** was obtained. This intermediate was subsequently treated with Fmoc-aminoacetaldehyde yielding **43** as a separable mixture of stereoisomers (25:75 according to TLC). The major diasteromer was readily isolated by flash chromatography. Attachment of thymine-1-yl acetic acid to the modified PNA backbone afforded **44**. Finally, the t-butyl group was removed by TFA scavenger and **14s** was obtained in a moderate yield.

Solid Phase Synthesis

Procedure a) O-Glycosylated PNA

A well-characterised decamer PNA was applied as an antibacterial agent (32). The thymine-based PNA monomers of the decamer were replaced with O-galactosylated PNA monomers (**1s-2s**). The high lability of O-glycosidic bonds necessitated the use of a mild method for solid phase synthesis of O-glycosylated PNA oligomers. The Fmoc strategy was applied, since it has been adapted to O-glycosyl peptide solid phase synthesis (33). The stability of the o-galactosylated PNA to acidic cleavage conditions was tested on several resins. The Fmoc-Sieber-TG resin was found suitable due to its susceptibility to mild cleavage conditions (2% TFA in DCM). The β-elimination of the sugar moiety during synthesis and deprotection steps was also investigated. The HATU-collidine was found the most suitable coupling reagent. HATU was neutralised with collidine prior to acid pre-activation. The deprotection was carried out by anhydrous 50% morpholine in DMF at the minimum time required for deprotection (10+5 min). Coupling completion was investigated by Kaiser test and capping was avoided. As a cleavage mixture, 5% water, 30% TFA in DCM was sufficient to cleave the BHOC groups. Finally, a methanolic hydrazine solution (pH 9.5) was applied for the post-cleavage de-acetylation of the sugar-residue.

Procedure b) Lysine-based -C, N, C-glycosylated PNA

Initially, the Boc-strategy for the solid phase synthesis of PNA oligomers containing lysine based c-glycosylated-PNA monomers was applied. In the case of oligomers containing one residue of **s5**, following cleavage with TFMSA, a side product consisting of oligomer minus.

one acetyl-group was detected by MALDI, and HPLC. Although the final deacetylation of both the product and the side product gave the target oligomer, it was decided to switch to the fmoc strategy, in order to avoid the use of strong acidic cleavage condition in boc strategy. For this purpose **22-24** was converted to the corresponding fmoc protected derivatives **5s-8s.** C-and N-glycosylated PNA monomers **9s-14s** were also prepared as fmoc protected derivatives. C- and N-glycosylated PNA monomers was also prepared as fmoc protected derivatives. PNA oligomers were synthesized on Fmoc-PAL-PEG resin. HATU-DIPEA was used as the coupling reagents and 20% piperidine in DMF at minimum required time for deprotections (3+2 min). Coupling yields were detected by Kaiser test and capping steps were avoided. A cleavage reagent of 5% TES in TFA was used and acetyl groups were removed with methanolic hydrazine (pH 10) solution following cleavage.

Several oligomers were synthesised and melting point temperature (Tm) values were determined by standard methods. All of glycosylated PNAs showed reasonable binding affinity.

c) Glycosylated PNAs having cysteine at the N-terminal

In order to develop the chemically conjugates of glycosylated PNA with biologically interesting compounds such as peptides or labelling compounds, it was necessary to optimise a method for the solid phase synthesis of the conjugate. For this purpose, cysteine was introduced at the N-terminal end of the glycosylated PNA as a S-trityl-protected derivative. Deprotection of sugar hydroxyl groups were performed on the resin prior to cleavage.

Eight decamers were prepared with incorporated glycosylated PNA monomers. The monomers were introduced in two or three residues shown as T* in Table 1.

Table 1

Cys-C-T***-C-A-T**-A-C-T*-C-T-NH_2

PNA No:	Incorporated monomer	Number of residues
PNA: 1	7s	T*, T**
PNA: 2	8s	T*, T**
PNA: 3	9s	T*, T**
PNA: 4	10s	T*, T**
PNA: 5	11s	T*, T**
PNA: 6	12s	T*, T**, T***
PNA: 7	13s	T*, T**, T***
PNA: 8	14s	T*, T**, T***

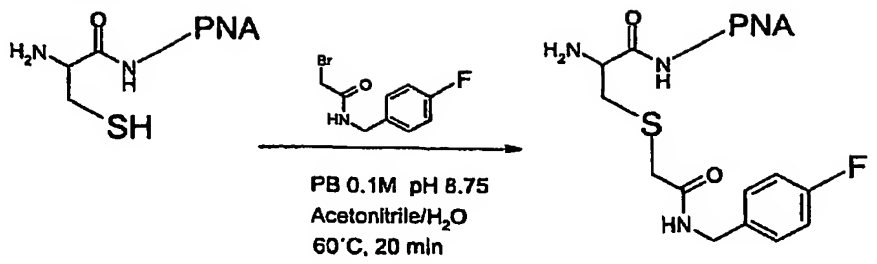
In-vivo imaging of glycosylated PNAs

Positron Emission Tomography (PET), a high-resolution sensitive and non-invasive imaging technique for the labelling of oligonucleotides (34) containing a single phosphorotioate monoester with an electrophilic moiety such as 2-bromo-N-substituted acetamides was applied. N-(4-halobenzyl)-2-bromoacetamide was designed as a radiochemically feasible reagent, the benzyl function offering the opportunity to act as the carrier of a radioactive halogen such as fluorine-18, the most widely used positron emitter ($T_{1/2}$ = 109,8 min.). Cysteine has a high and selective reactivity towards N-(4-fluorobenzyl)-2-bromoacetate, due to its nucleophilic thiol function. Based hereupon, eight glycosylated PNA decamers (shown in table 1) were prepared.

a) Synthesis of non-radioactive references

PNA monomers were conjugated with N-(4-fluorobenzyl)-2-bromoacetamide in a mixture of acetonitrile and phosphate buffer (0,1 M aq., pH 8.75) for 20 minutes at 60°C (scheme 8). The conjugated PNAs were purified by semi-preparative reverse phase HPLC and characterised by mass spectroscopy analysis (MALDI-TOF).

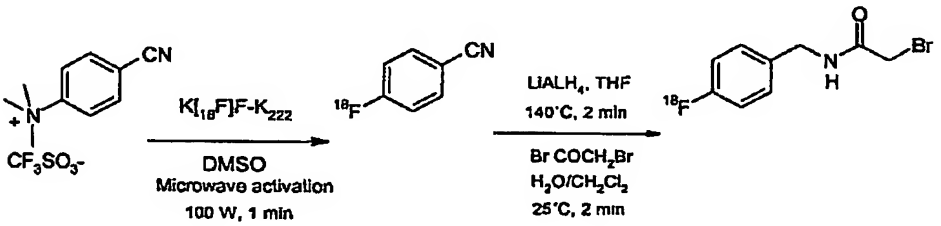
Scheme 8



b) Radiochemistry

N-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide was synthesised in three steps using a robot. Typically, 60-90 mCi of pure N-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide was obtained in 85-95 min. starting from a 550-650 mCi of a cyclotron [^{18}F]F- production batch (scheme 9).

Scheme 9



The HPLC-collected fraction containing N-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide was concentrated to dryness at 80°C under a nitrogen stream, before diluted with 0.4 ml acetonitrile. A solution of 1.3 mg PNA in 0.5 ml phosphate buffer (0.1 M, pH 8.75) and 0.1 ml of acetonitrile was rapidly added. The reactor was placed in a heating block and heated without stirring under a slight flow of nitrogen at 60°C for 20 minutes. Before total dryness, 1 ml distilled water was added to the reaction mixture, and the suspension was subjected to the HPLC purification for separation of labelled PNA[^{18}F], unreacted PNA and unreacted N-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide. Labelled PNAs co-eluted with authentic synthesized unlabelled reference compounds. The HPLC fraction containing the labelled PNA was concentrated and formulated by transferring into a volume of 1-2 ml of serum.

c) In-vivo PET imaging

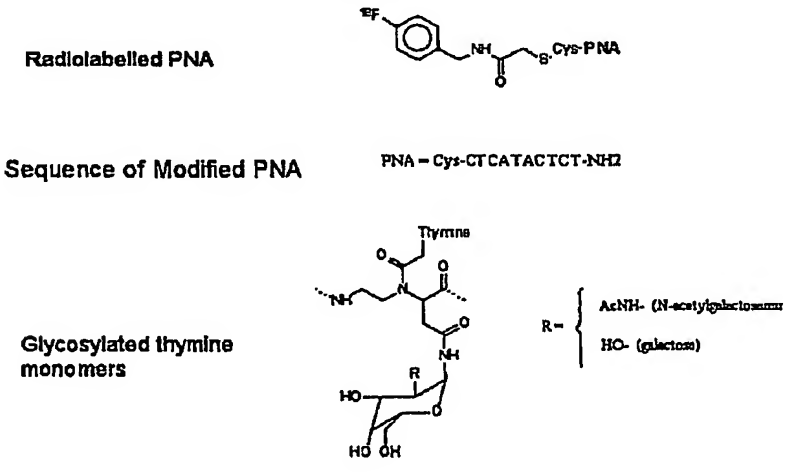
Two male and two female Spargue-Dawley rats (200 g) were injected with 40 mCi labelled PNA in the tail vein placed in a Siemens ECAT EXACT HR+ camera under anesthesia and whole body images acquired in 3D mode for 2 hours.

d) Ex-vivo study of bio-distribution

Following imaging, the animals were sacrificed and the kidneys, liver, spleen, heart, lungs, brain, muscles, blood and adrenals immediately collected. Aliquots of these organs were weighed and radioactivity was counted on a radiocounter. Radioactivity was expressed as percentage of injected dose per gram of organ (%ID/g) and reported as the mean ± standard deviation.

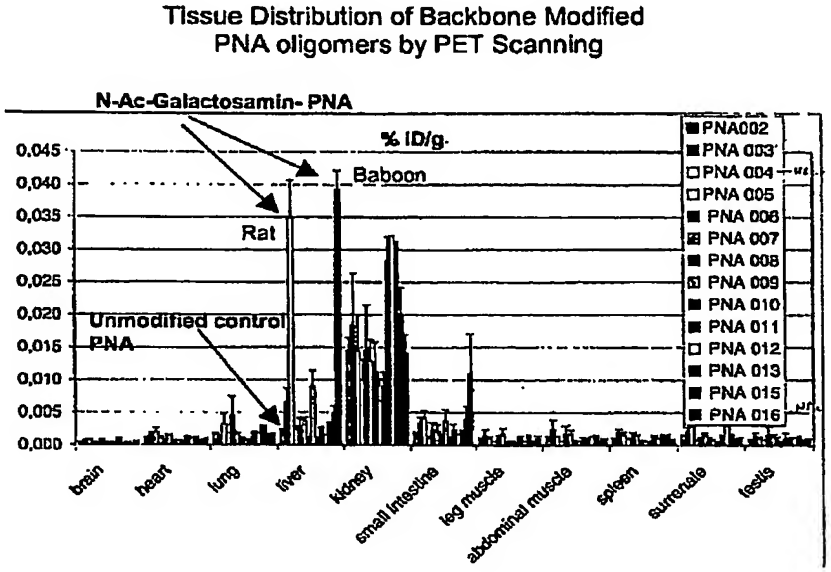
Example of PNA oligomers containing glycosylated monomers used for pharmacokinetic analyses by ^{18}F-isotope PET scanning is shown in Figure 1:

Figure 1



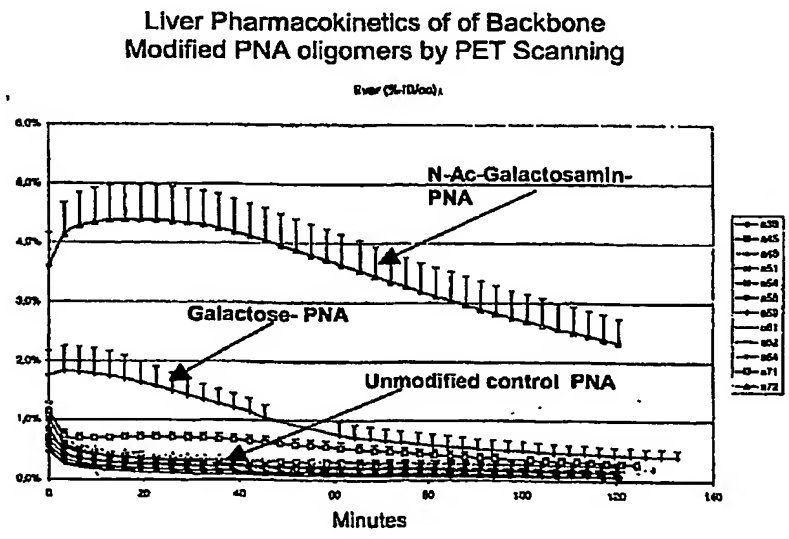
Organ distribution of PNA oligomers in rats is shown in Figure 2. The N-acetyl-galacotsamine PNA shown in Figure 2 is preferentially targeting the liver. Similar results were obtained in baboons.

Figure 2



Pharmacokinetics of PNA oligomers of the type shown in figure 1 analysed by PET scanning. The N-acetyl-galacotsmine PNA shown in Fig. X is preferentially accumulated in the liver. Similar results were obtained baboons.

Figure 3



e) Study of metabolism

Plasma supernatants were centrifuged in microfilter/10000 fixed Eppendorf tubes and subjected to analytical RP-HPLC. Urine samples were subjected to the HPLC directly. In some cases the samples were co-injected with unlabelled PNA.

Pharmaceutical Compositions

The PNA drugs of the present invention are used in the manufacture of medicaments for the treatment or prevention of bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune and immunological disorders, or for disinfecting non-living objects, such as surgery tools, hospital inventory, dental tools, slaughterhouse inventory and tool, dairy inventory and tools, barbers and beauticians tools and the like.

Within the present invention, the compounds of the invention may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric- and phosphoric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, Berge et al 1977 (19), which are known to the skilled artisan.

Also intended as pharmaceutically acceptable acid-addition salts are the hydrates, which the present compounds are able to form.

The acid-addition salts may be obtained as the direct drugs of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

In one aspect, the invention concerns the manufacture of a composition for treating or preventing bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune and immunological disorders, or disinfecting non-living objects, such as surgery tools, hospital inventory, dental tools, slaughterhouse inventory and tool, dairy inventory and tools, barbers and beauticians tools and the like.

Typical compositions include a compound of the invention or a pharmaceutically acceptable acid-addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier, which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material, which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohol's, polyethylene glycol's, polyhydroxyethoxylated castor oil, peanut oil, olive oil, glycine, gelatin, lactose, terra alba, sucrose, glucose, cyclodextrine, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, thickeners or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For therapeutic or prophylactic treatment, the PNA drug of the invention can be formulated in

a pharmaceutical composition, which may include one or more active ingredients such as antimicrobial agents, anti-inflammatory agents, anaesthetics, and the like in addition to PNA.

The pharmaceutical composition may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated. Administration may be done topically (including ophthalmically, vaginally, rectally, intranasally), orally, by inhalation, or parenterally, for example by intravenous drip or subcutaneous, intraperitoneal or intramuscular injection.

Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms may also be useful.

Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavourings, diluents, emulsifiers, dispersing aids or binders may be desirable.

If a solid carrier is used for oral administration, the preparation may be tabletted placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a suspension or solution in water or a non-aqueous media, a syrup, emulsion or soft gelatin capsules. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be added.

Formulations for parenteral administration may include sterile aqueous solutions, which may also contain buffers, diluents and other suitable additives.

For nasal administration, the preparation may contain a compound of the invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilising agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrine, or preservatives such as parabenes.
For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

In yet another aspect, the invention concerns the treatment or prevention of bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune and immunological disorders, or treatment of non-living objects.

Dosing is dependent on severity and responsiveness of the condition to be treated, but will normally be one or more doses per day, with course of treatment lasting from several days to several months or until a cure is effected or a diminution of disease state is achieved. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.01 mg to about 500 mg, preferably from about 0.01 mg to about 100 mg of the compounds of the invention admixed with a pharmaceutically acceptable carrier or diluent.

Treatments of this type can be practiced on a variety of organisms ranging from unicellular prokaryotic and eukaryotic organisms to multicellular eukaryotic organisms. Any organism that utilises DNA-RNA transcription or RNA-protein translation as a fundamental part of its hereditary, metabolic or cellular control is susceptible to therapeutic and/or prophylactic treatment in accordance with the invention. Seemingly diverse organisms such as bacteria, yeast, protozoa, algae, all plants and all higher animal forms, including warm-blooded animals, can be treated. Further, since each cell of multicellular eukaryotes can be treated since they include both DNA-RNA transcription and RNA-protein translation as integral parts of their cellular activity. Furthermore, many of the organelles, (e.g. mitochondria and chloroplasts) of eukaryotic cells also include transcription and translation mechanisms. Thus, single cells, cellular populations or organelles can also be included within the definition of organisms that can be treated with therapeutic or diagnostic PNA drug. As used herein, therapeutics is meant to include the eradication of a disease state, by killing an organism or by control of erratic or harmful cellular growth or expression.

EXPERIMENTAL

The following examples are merely illustrative of the present invention and should not be considered limiting of the scope of the invention in any way.

Abbreviations

The following abbreviations related to reagents are used in the experimental part:

Aeg-PNA	Amino Ethyl Glycine-PNA alias unmodified PNA
A monomer	N-(2-Boc-aminoethyl)-N-(N^6-(benzyloxycarbonyl)adenine-9-yl-acetyl)glycine
Boc	Tert butyloxycarbonyl
Boc-Lys(2-Cl-Z)-OH	N-α-Boc-N-ε-2-chlorobenzyloxycarbonyl-L-lysine
C monomer	N-(2-Boc-aminoethyl)-N-(N^4-(benzyloxycarbonyl)cytosine-1-yl-acetyl)glycine
TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
DIC	Diisopropylcarbodiimide
HOBt	N-Hydroxybenzotriazole
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIEA	N,N-diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
G monomer	N-(2-Boc-aminoethyl)-N-(N^2-(benzyloxycarbonyl)guanine-9-yl-acetyl)glycine
HATU	N-[(1-H-benzotriazole-1-yl)(dimethylamine)methylene]-N-methylmethanaminiumhexafluorophosphate N-oxide
HBTU	2-(1-H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
J monomer /nucleobase	N-(2-Boc-aminoethyl)-N-(N-2-(benzyloxycarbonyl) isocytosine-5-yl-acetyl)glycine
MBHA resin	p-methylbenzhydrylamine resin
NMP	N-methyl pyrrolidone

PTSA	Para - Toluene sulphonic Acid
T monomer	N-(2-Boc-aminoethyl)-N-(thymine-1-yl-acetyl)glycine
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TFMSA	Trifluoromethanesulphonic acid
Tris	2-amino-2-(hydroxymethyl)-1,3-propanediol

Amino Acid	**Abbr. I**	**Abbr. II**	**Side Chain Group**
Alanine	A	Ala	methyl
Arginine	R	Arg	3-guanidinopropyl
Aspartic acid	D	Asp	carboxymethyl
Asparagine	N	Asn	aminocarboxymethyl
Cysteine	C	Cys	mercaptomethyl
Glutamic acid	E	Glu	2-carboxyethyl
Glutamine	Q	Gln	aminocarboxyethyl
Histidine	H	His	imidazol-4-yl-methyl
Isoleucine	I	Ile	1-methylpropyl
Leucine	L	Leu	2-methylpropyl
Lysine	K	Lys	4-aminobutyl
Methionine	M	Met	2-(methylthio)ethyl
Phenylalanine	F	Phe	benzyl
Serine	S	Ser	hydroxymethyl
Threonine	T	Thr	1-hydroxyethyl
Tryptophan	W	Try	3-indolyl
Tyrosine	Y	Tyr	4-hydroxybenzyl
Valine	V	Val	1-methylethyl
Homoserine	-	(Hse)	2-hydroxymethyl
Citrulline	-	(Cit)	3-ureidopropyl
4-pyridyl-alanine	-	(4-Py)	4-pyridomethyl

Reagents and solvents were obtained from commercial sources and used without further purification, unless indicated. NMR spectra were recorded in $CDCl_3$ and CD_3OH on Varian 400, 300 MHz and Brucher 250 MHz unity spectrometers, FAB mass spectra on a JEOL HX 110/110 mass spectrometer, MALDI-TOF mass spectra on a Cratos Compact Maldi II spec-

trometer. The Microanalysis Department of HCØ Institute, University of Copenhagen, performed elementary analyses. Flash chromatography was carried out using Silica Gel 60 (Merck particle size 0.040-0.063mm). The oligomers were analysed on a Delta Pak C_{18} column (5µM, 3.9x150mm) and were purified on a Delta Pak C_{18} column (15µM, 19x300mm). A gradient composed of A (0.1%TFA in water) and B (0.1% TFA in 10% H_2O/90% acetonitrile) was used for analytical and preparative HPLC. Analytical: Time 0, 0% B. Time 35 min, 50% B (Flow, 1ml/min). Preparative: Time 0, 15% B. Time 45 min, 40% B (Flow, 8ml/min).

EXAMPLE 1

Procedure (a): allylation of N-protected amino acids

5 mmol of *N*-protected aminoacid was dissolved in a mixture of 10 ml acetonitrile and 12 ml allylbromide. (2.1 eq) N-N-diisopropylethylamine was added and the reaction mixture was stirred for 4 h at 40°C. Subsequently 200 ml ethylacetate was added and the solution was extracted with half saturated $KHSO_4$ (2 x 50 ml) and half saturated $NaHCO_3$ (2 x 50 ml) and 100 ml brine respectively. Organic phase was dried over $MgSO_4$ and volatile were removed under vacuum. The remaining oil was used for the next step (Yield = 87%-95%).

EXAMPLE 2

Procedure (b): preparation of N-boc/fmoc protected PNA backbone

12 mmol amine and 10 mmol boc/fmoc-aminoacetaldehyde were stirred in 40 ml methanol for 10 min. 0.8 ml (13 mmol) Acetic acid and 0.6 g (10 mmol) natrium cyanoborohydrate was added sequentially. The reaction mixture was stirred for further 1 h at room temperature. Volatiles was removed under vacuum and the remaining solid dissolved in 100 ml ethyacetate and extracted with $NaHCO_3$ saturated solution and brine. Organic phase was dried over magnesium sulphate and evaporated to dryness under vacuum. The residue was purified on silica gel column eluting hexane-ethylacetate 1:1. (Yield = 50% - 80%).

EXAMPLE 3

Procedure (c): coupling of thymine-1-yl-acetic acid to the PNA backbone

17 mmol Thymine-1-ylacetic acid and 18 mmol DhbtOH were dissolved in 50 ml dry DMF. 20 mmol DCC was added and the solution stirred for 20 minutes. 8.5 mmol backbone was added in 20 ml dry DMF to the reaction mixture and stirred for further 6 h at room temperature. Volatiles were removed under vacuum and the remaining dissolved in 200 ml ethylacetate. Insoluble DCU was filtered off and the filtrate extracted with $NaHCO_3$ saturated solution (2 x 100 ml) and brine (100 ml). After drying over magnesium sulphate, the organic phase

was evaporated to dryness. The residue was purified on a silica gel column eluting the mixture of ethylacetate-methanol 10:0 to 10:1 (Yield = 63%-87%).

EXAMPLE 4

Procedure (d): boc de-protection and subsequent fmoc protection

3 mmol boc-protected compound was added to 20 ml solution of 5% triethylsilane in trifluoroacetic acid at 0°C and stirred until TLC did not show any starting material left. 50 ml Toluene was added and volatile removed under vacuum. Further 3 x 100 ml DCM was added and evaporated in order to removal of TFA. The remaining was dissolved in 50 ml diethylether and 5 g natrium carbonate was added as well powdered solid. The suspension was stirred for 30 min and then evaporated. The solid residue was suspended in 50 ml Acetonitrile and 3.2 mmol fmoc-O-Su was added and stirred for further 2h. The solution was evaporated under vacuum and the crude was purified on silica gel column eluting ethylacetate-methanol 10:0 to 10:1 (Yield = 88%-94%).

EXAMPLE 5

Procedure (e): N-glycosylation

2 mmol **32**, 2.2 mmol DhbtOH, and 3 mmol DCC were mixed in 10 ml DMF and stirred for 30 min under Nitrogen. A solution 2 mmol Sugar-amine in 10 ml DMF was added and the reaction mixture was stirred overnight. Volatile was removed under vacuum and the residue dissolved in 200 ml ethylacetate. Insoluble DCU was filtered off and the filtrate extracted with $NaHCO_3$ saturated solution (2 x 100ml) and brine (100 ml). After drying over magnesium sulphate the organic phase was evaporated to dryness. The residue subjected to silica gel column eluting the mixture of ethylacetate-methanol 10:0 to 10:1 (Yields = 60%-77%).

EXAMPLE 6

Procedure (f): removing of allyl group

0.1 mmol of ester was dissolved in 2 ml THF. 23 mg (0.02 mmol, 0.2 eq) Tetrakis(triphenylphosphine)Pd(0) was added. 10 eq N-ethyl-aniline was added drop wise to the reaction mixture and stirred at room temperature. The reaction was checked by TLC (ethylacetate-methanole 10:1). After complete conversion of starting material, the reaction mixture was poured dropwise in a 20 ml vigorously stirring solution of diethylether-n-hexane 1:1. White precipitate was collected by filtration and washed with n-hexane (Yield = 80%-95%).

EXAMPLE 7

Threonine(t-Bu)-Allyl (4)

To 4.4 g (10 mmol) **2** [prepared by *procedure (a)*] was added 50 ml of a solution of 20% piperidine in DCM. After 30 min, 100 ml toluene was added and volatile were removed under vacuum. The residue was purified with a short silica gel column eluting ethylacetate-methanole 10:0 to 10:1. 1.6 g (7.5 mmol) titled compound was obtained as colourless oil (Yield = 75%).

[α] obtained as colourless oil in 83% yield.

$[\alpha]_D^{22}$ = -1.53 (*c* = 1, methanol); MS (FAB) *m/z* 216 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 5.94 (9 line m, 1H, -C<u>H</u>=CH_2), 5.3 (dd, 1H, J_{trans} = 17.03, 1.37 Hz), 5.2 (dd, 1H, J_{cis} = 10.5, 1.1 Hz), 4.64-4.46 (dddt, 2H, J = 33.08, 10.7, 5.8, 1.1, O-C<u>H_2</u>-CH=), 4 (m, 1H, $^{\beta}$CH), 3.26 (d, 1H, J=3.3 Hz, $^{\alpha}$CH), 1.65 (s, 2H, -NH_2), 1.2 (d, 3H, J=6.3 Hz, $^{\beta}$C-CH3), 1.09 (s, 9H, boc); ^{13}C-NMR ($CDCl_3$): δ 174.51 (COO-Allyl), 132.09 (-<u>C</u>H=CH_2), 118.87 (-CH=<u>C</u>H_2), 73.77 [-O-<u>C</u>(Me)$_3$], 68.63, 65.67, 60.84, 28.68 [-COO-C(<u>C</u>H_3)$_3$], 20.94 ($^{\beta}$C-<u>C</u>H_3).

C.H.N analyse for $C_{11}H_{21}NO_3$. ½ H_2O: calc. C 60.11, H 9.86, N 6.37; found C 59.87, H 9.95, N 6.34.

EXAMPLE 8

***N*-(2-Boc-aminoethyl)-Serine(t-Bu)-Allyl (5)**

Preparation: Procedure (b)

$[\alpha]_D^{22}$= -10.26 (*c*=1, methanol); MS (FAB) *m/z* 345(M+H); ^{1}H-NMR, ($CDCl_3$): δ 5.96-5.89 (8 line m, 1H, -C<u>H</u>=CH_2), 5.26 (dd, 1H, J_{trans}=17.2, 1.46 Hz), 5.17 (dd, 1H, J_{cis}=10.4, 1.28 Hz), 5.05 (br.s, boc-HN-), 4.57-4.55 (m, 2H, O-C<u>H_2</u>-CH=), 3.52 (ABq, 2H, J=4.95Hz, $^{\beta}$CH), 3.36 (t, J=4.76 Hz, 1H, $^{\alpha}$CH), 3.2-3.1 (m, 2H), 2.8 (m, 1H), 2.6 (m, 1H), 1.37 (s, 9H, *t*-butyl), 1.08 (s, 9H, boc); ^{13}C-NMR ($CDCl_3$): δ 172.50 (COO-Allyl), 155.9 (-NH-COO), 131.74 (-<u>C</u>H=CH_2), 118.42 (-CH=<u>C</u>H_2), 118.27, 73.13 [-O-<u>C</u>(Me)$_3$], 65.263 (-<u>C</u>H_2-CH=), 62.66 (β carbon), 61.22 (α carbon), 47.18, 40.03, 28.25 [-COO-C(<u>C</u>H_3)$_3$], 27.17 [-O-C(<u>C</u>H_3)$_3$].

C.H.N analyse for $C_{17}H_{32}N_2O_5$. ½ H_2O: calc. C 57.77, H 9.41, N 7.93; found C 58.11, H 9.20, N 8.14.

EXAMPLE 9

***N*-(2-Boc-aminoethyl)-Threonine(t-Bu)-Allyl (6)**

Preparation: Procedure (b)

(Yield = 67%) $[\alpha]_D^{22}$= -3.39 (*c*=1, methanol); MS (FAB) *m/z* 359 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 5.90-5.83 (8 line m, 1H, -C<u>H</u>=CH_2), 5.26 (dt, 1H, J_{trans}=17, 1.4 Hz), 5.18 (dt, 1H, J_{cis}=10, 1.1

Hz), 5.05 (br.s, boc-HN-), 4.60-4.47 (dddt, 2H, J=33.3, 13.2, 5.8, 1.3 HZ, O-C$\underline{H}_2$-CH=), 3.9 (q, 1H, $^{\beta}$CH), 3.14-3.08 (dm, 2H), 3.05 (d, 1H, J=3.5, $^{\alpha}$CH), 2.8 (m, 1H), 2.7 (m, 1H), 1.37 (s, 9H, *t*-butyl), 1.18 (d, 3H, J=6.2 Hz, $^{\beta}$C-CH3), 1.06 (s, 9H, boc); ^{13}C-NMR ($CDCl_3$): δ 172.91 (COO-Allyl), 155.88 (-NH-COO), 131.65 (-$\underline{C}$H=CH_2), 118.54 (-CH=$\underline{C}H_2$), 78.81 [-COO-$\underline{C}$(Me)$_3$], 73.66 [-O-$\underline{C}$(Me)$_3$], 68.14 (β carbon), 66.37 (α carbon), 65.270 (-$\underline{C}H_2$-CH=), 47.51, 39.88, 28.23 [-COO-C($\underline{C}H_3$)$_3$], 28.19 [-O-C($\underline{C}H_3$)$_3$], 20.49 ($^{\beta}$C-$\underline{C}$H3).

C.H.N analyse for $C_{18}H_{34}N_2O_5$: calc. C 60.31, H 9.56, N 7.81; found C 60.16, H 9.98, N 7.75.

EXAMPLE 10

***N*-(2-Boc-aminoethyl)-*N*-(Thymine-1-ylacetyl)Serine(t-Bu)-Allyl (7)**

Preparation: Procedure (c)

Mp = 70-72; MS (FAB) *m/z* 216 (M+H); ^{1}H-NMR, ($CDCl_3$): (major rotamer) δ 9.08 (s, 1H, Thymine aromatic), 6.83 (s, 1H, Thymine-NH-), 5.87-5.77 (8 line m, 1H, -C$\underline{H}$=CH_2), 5.6 (br.s, 1H, boc-HN-), 5.25 (dd, 1H, J_{trans}=17.2, 1.28 Hz), 5.17 (dd, 1H, J_{cis}=10.2, 0.91 Hz), 4.6-4.4 (dm, 2H, -O-C$\underline{H}_2$-CH=), 4.55 (s, 2H, -CO-CH2-Thymine), 4.26 (br.d, 1H, J=5.3), 3.93 (t, 1H), 3.77 (dd, 1H, J=10, 3.1 Hz), 3.6-3.4 (dm, 2H), 3.35 (m, 2H), 1.83 (s, 3H, Thymine-CH_3), 1.37 (s, 9H, *t*-butyl), 1.1 (s, 9H, boc); ^{13}C-NMR ($CDCl_3$): δ 168.93, 167.15, 164.07, 155.85 (-NH-COO), 150.72, 140.72, 131.36 (-$\underline{C}$H=CH_2), 118.84 (-CH=$\underline{C}H_2$), 111.59, 110.43, 79.62 [-COO-$\underline{C}$(Me)$_3$], 73.84 [-O-$\underline{C}$(Me)$_3$], 66.06 (-$\underline{C}H_2$-CH=), 60.79, 60.24, 59,50, 38.84, 33.66, [28.30, 28.10, -COO-C($\underline{C}H_3$)$_3$], 27.15 [-O-C($\underline{C}H_3$)$_3$], 12.25 (Thymine-CH_3).

EXAMPLE 11

***N*-(2-Boc-aminoethyl)-*N*-(Thymine-1-ylacetyl)Threonine(t-Bu)-Allyl (8)**

Preparation: Procedure (c)

Mp = 71-73; Yield = 76%; MS (FAB) *m/z* 525(M+H); ^{1}H-NMR, ($CDCl_3$): (major rotamer) δ 8.59 (s, 1H, Thymine aromatic), 6.9 (s, 1H, Thymine-NH-), 5.95-5.85 (8 line m, 1H, -C$\underline{H}$=CH_2), 5.5 (br.s, 1H, boc-HN-), 5.3 (dd, 1H, J_{trans}=17.1, 1.4 Hz), 5.25 (d, 1H, J_{cis}=10.2 Hz), 4.66 (s, 2H, -CO-CH2-Thymine), 4.52-4.41 (overlapping m, 3H, -O-C$\underline{H}_2$-CH=, $^{\alpha}$CH), 4.1 (q, 1H), 3.8 (dt, 1H, J=15.3, 6 Hz), 3.6 (m, 1H), 3.5-3.4 (m, 2H), 1.89 (s, 3H, Thymine-CH_3), 1.44 (s, 9H, *t*-butyl), 1.28 (d, 3H, J=6Hz, -$^{\beta}$C-CH_3). 1.1 (s, 9H, boc); ^{13}C-NMR ($CDCl_3$): (major rotamer) δ 169.12, 167.95, 163.78, 155.78 (-NH-COO), 150.59, 140.73, 131.20 (-$\underline{C}$H=CH_2), 119.41 (-CH=$\underline{C}H_2$), 110.43, 79.61 [-COO-$\underline{C}$(Me)$_3$], 74.55 [-O-$\underline{C}$(Me)$_3$], 66.14 (-$\underline{C}H_2$-CH=), 64.39, 39.16, 33.79, [28.69, 28.60, 28.40, -COO-C($\underline{C}H_3$)$_3$], [25.53, 24.87, -O-C($\underline{C}H_3$)$_3$], 21.71 ($^{\beta}$C-$\underline{C}H_3$), 12.37 (Thymine-CH_3).

EXAMPLE 12

_N_-Fmoc-aminoethyl-_N_-(Thymine-1-ylacetyl)Serine(OH)-Allyl (11)

Preparation: Procedure (d)

Mp = 101-103; $[\alpha]_D^{22}$= -5.36 (*c*=0.25, methanol); MS (FAB) *m/z* 577(M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.63 (s, 1H,Thymine aromatic), 7.56-7.07 (8H, Florenyl aromatic protons), 6.59 (s, 1H, Thymine-NH-), 5.9 (s, 1H, fmoc-HN-), 5.8-5.6 (m, 1H, -C<u>H</u>=CH_2), 5.12 (d, 1H, J_{trans}=17.2 Hz), 5.05 (dd, 1H, J_{cis}=10.4, 0.91 Hz), 4.6-4.4 (m, 3H, O-C<u>H_2</u>-CH=, $^{\alpha}$CH), 4.24 (s, 2H, -CO-CH2-Thymine), 4-3.8 (m, 4H), 3.4-3.2 (m, 4H), 2.73 (br.s, 1H), 1.7 (s, 3H, Thymine-CH_3); ^{13}C-NMR ($CDCl_3$): δ 168.50, 168.06, 167.94, 167.07, 164.05, 162.58, 156.59, 151.33, 143.58 and 143.39 (florenyl), 140.98, 131.14 (-<u>C</u>H=CH_2), [(130.69, 127.54, 126.88, 124.82, 124.36, 119.75 (florenyl)], 118.95 (-CH=<u>C</u>H_2), 110.90, 66.75, 66.17, 63.43 (-<u>C</u>H_2-CH=), 59.47, 49.24, 48.81, 47.10, 39.45, 31.54, 12.30 (Thymine-CH_3).

C.H.N analyse for $C_{30}H_{32}N_4O_8$. ½ H_2O: calc. C 61.35, H 5.68, N 9.57; found. C 61.39, H 5.53, N 9.36.

EXAMPLE 13

_N_-Fmoc-_N_-(Thymine-1-ylacetyl)Threonine(OH)-Allyl (12)

Preparation: Procedure (d)

Mp = 99-101; Yield = 91%; $[\alpha]_D^{22}$= -0.93 (*c*=0.75, methanol); MS (FAB) *m/z* 591 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 8.9 (s, 1H,Thymine aromatic), 7.6-7.1 (8H, Florenyl aromatic protons), 6.6 (s, 1H, Thymine-NH-), 5.8-5.6 (overlapping m, 2H, -C<u>H</u>=CH_2, fmoc-HN-) 5.12 (dt, 1H, J_{trans}=16.1, 8.8 Hz), 5.07 (dd, 1H, J_{cis} = 10.3, 1 Hz), 4.5 (overlapping m, 3H), 4.42-4.26 (m, 2H, O-C<u>H_2</u>-CH=), 4.2 (t, 1H, J=7.4 Hz) 4.03 (d, 2H, J=6 Hz), 3.65 (br.d, 1H, J=5.3 Hz), 3.53-3.47 (m, 1H), 3.4-3.24 (m, 3H), 2.8 (br.s, 1H), 1.68 (s, 3H, Thymine-CH_3), 1.14 (d, 3H, J=5.86 Hz, -$^{\beta}$C-CH_3); ^{13}C-NMR ($CDCl_3$): δ 168.67, 167.85, 163.99, 156.60, 151.10, [143.67, 143.50, 141.15, 140.98 (florenyl)], 131.22 (-<u>C</u>H=CH_2), 127.64, 126.96, 124.88, 124.36, 119.87, 119.25 (-CH=<u>C</u>H_2), 110.75, 67.50, 66.61, 66.19, 65.16, 49.55, 48.86, 47.06, 39.41, 21.30 ($^{\beta}$C-<u>C</u>H_3), 12.30 (Thymine-CH_3).

C.H.N analyse for $C_{31}H_{34}N_4O_8$. ½ H_2O: calc. C 62.09, H 5.88, N 9.34; found C 62.10, H 5.86, N 9.22.

EXAMPLE 14

_N_-Fmoc-_N_-(Thymine-1-ylacetyl)Serine(2,3,4,5-tetra-_O_-acetyl-α-D-Galactose-1-yl)-Allyl (13)

Preparation: 0.7g (1.2 mmol) **11** and 0.75 g (1.5 mmol) galactose trichloroacetamide were dissolved in 5 ml ethylacetate. 0.5 g molecular sieve was suspended and 1.2 ml (9.5 mmol) borontriflate in 1 ml ethylacetate was added at 0°C. Ice bath was removed and the reaction mixture was stirred under nitrogen over night. 50 ml ethylacetate was added and the reaction mixture was filtered over celite. The filtrate was extracted with an ice cold half saturated $NaHCO_3$ aqueous solution (2 x 25 ml), and brine (50 ml), dried over magnesium sulphate and evaporated to dryness. The residue was purified on silica gel column eluting hexane-ethylacetate 1:1. 0.4 g (0.9 mmol) α anomer was obtained as white crystalline.(yield = 37%) Mp = 115-118; $[\alpha]_D^{22}$= -24.17 (*c*=0.5, methanol); MS (FAB) *m/z* 907(M+H); ^{1}H-NMR, ($CDCl_3$): δ 8.75 (s, 1H, Thymine aromatic), 7.68-7.21 (m, 8H, Florenyl aromatic protons), 6.8 (s, 1H, Thymine-NH-), 5.9-5.7 (overlapping m, 2H, -C<u>H</u>=CH_2, fmoc-HN-), 5.3(d, 1H, J=2.9 Hz, sugar ^{4}CH), 5.25 (d.d, 1H, J_{trans} = 17.2, 1.26 Hz), 5.15 (d, 1H, J_{cis}=10.7 Hz), 5.05 (t, 1H, $J_{1,2}$=7.7 Hz, $J_{2,3}$=10.4 Hz, sugar ^{2}CH), 4.95 (dd, 1H, J=10.4, 3.2 Hz, sugar ^{3}CH), 4.7-4.3 (m, 6H), 4.25, 3.95 (m, 6H), 3.8 (t, 2H, J=6.4, sugar ^{5}CH), 3.6-3.3 (m, 3H), 2.9 (br.s, 1H), 2.1-1.9 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ^{13}C-NMR ($CDCl_3$): δ 169.37, 169.09, 168.96, 168.80, 166.84, 166.61, 163.09, 155.81(-NH-COO), 149.67, 142.76, 140.27, 130.37 (-<u>C</u>H=CH_2), 126.73, 126.06, 123.91, 118.98, 118.24 (-CH=<u>C</u>H_2), 109.26, 100.03 (sugar C1), 70.09, 69.57, 67.75, 66.38, 65.93, 65.54, 65.43, 60.22, 60.09, 47.48, 47.02, 46.29, 38.60, 19.78-19.54 (sugar-CO-<u>C</u>H_3 groups), 11.28 (Thymine-CH_3).

HRMS $(M+Na)^+$, calculated (found) for $C_{44}H_{50}N_4O_{17}Na$ are 929.3069 (929.3087).

EXAMPLE 15

N-Fmoc-N-(Thymine-1-ylacetyl)Threonine(2,3,4,5-tetra-O-acetyl-α-D-Galactose-1-yl)-Allyl (14)

Preparation: The Procedure is the same as described above for the synthesis of **13**
Yield = 77%, mp = 106-108; $[\alpha]_D^{22}$= -27.38 (*c*=0.5, methanol); MS (FAB) *m/z* 921(M+H); ^{1}H-NMR, ($CDCl_3$): δ ^{1}H-NMR, ($CDCl_3$): δ 8.54 (s, 1H,Thymine aromatic), 7.78-7.76 (8H, Florenyl aromatic protons), 6.95 (1H, Thymine-NH-), 5.92-5.82 (m, 1H, -C<u>H</u>=CH_2), 5.81 (s, 1H, fmoc-HN-), 5.38 (d, 1H, J=2.5 Hz, sugar ^{4}CH), 5.3 (d, 1H, J_{trans}=17.4 Hz), 5.2 (d, 1H, J_{cis}=10.4 Hz), 5.08 (t, 1H, $J_{1,2}$=7.7 Hz, $J_{2,3}$=10.4 Hz, sugar ^{2}CH), 5.03 (dd, 1H, J=10.4, 3.3 Hz, sugar ^{3}CH), 4.9 (d, 1H, J=16.3), 4.7-4.5 (overlapping s ddd and s, 4H, J=49.6, 13.2, 5.86 Hz, -O-C<u>H</u>$_2$-CH and CO-CH_2-Thymine), 4.44 (overlapping, 2H), 4.35 (d, 2H, J=16.3 Hz), 4.2(t, 2H, J=7 Hz), 4.07 (dd, 1H, J=22.9, 6.41 Hz, sugar ^{6}CH), 3.88 (dd, 1H, $J_{5,6}$=6.23Hz, $J_{5,6'}$=6.59, sugar ^{5}CH), 3.6 (overlapping s, 2H), 3.43 (br.s, 1H), 2.18-2 (3s, 12H, sugar acetyl protons), 1.88 (s, 3H, Thymine-CH_3), 1.27 (d, 3H, J=5.86, ^{β}C-CH_3); ^{13}C-NMR ($CDCl_3$): δ 170.11, 169.89, 167.97,

163.65, 156.64(-NH-COO), 150.35, 143.53, 141.21, 141.05, 131.31(-CH=CH_2), 127.51, 126.82, 124.78, 119.80, 118.78 (-CH=CH_2), 110.07, 98.73 (sugar C1), 73.34, 71.53, 70.70, 70.48, 70.01, 68.80, 66.66, 66.55, 66.17, 65.65, 64.10, 62.79, 60.84, 60.31, 48.48, 47.19, 39.70, [21.05, 20.83, 20.67, 20.55 (sugar-CO-CH3 groups)], 17.38, 14.20 ($^{\beta}$C-CH3), 12.29 (Thymine-CH_3).

C.H.N analyse for $C_{45}H_{52}N_4O_{17}$. H_2O: calc. C 57.56, H 5.80, N 5.97; found C 57.51, H 5.52, N 5.82.

EXAMPLE 16

Lysine(Dde)-Allyl (16)

Preparation: 5.7g (10 mmol) ester **15** [prepared by *Procedure (a)*] was added to a solution of 20% piperidine in DCM and stirred for 30 min. 100 ml toluene was added and volatile were removed under vacuum. The residue was purified on a short silicagel column eluting ethylacetate-methanole 10:0 to 10:1. 2.5 g (7 mmol) Titled compound was obtained as slightly yellow oil which was used subsequently for the next step (Yield = 71%).

MS (FAB) *m/z* 351(M+H); ^{1}H-NMR, ($CDCl_3$): δ 13.34(s, 1H, -HN-Dde), 5.9-5.8 (ddt, 1H, J=5.57, 10.55, 10.43 Hz, -CH=CH_2), 5.27(dd, 1H, J_{trans}=17.3, 1.47 Hz), 5.22(dd, 1H, J_{cis}=10.5, 1.17 Hz), 4.56 (dt, 5.86, 1.17Hz, O-CH_2-CH=), 3.4 (dd, 1H, J=7.5, 5 Hz, $^{\alpha}$CH), 3.3 (ABq, 2H, J_{AB}=12.3, -CH_2-NH-Dde), 2.49 (s, 3H, -HN-C-CH_3), 2.3 (s, 4H, 2x-CH_2- of Dde), 1.77 (s, 2H, -NH_2), 1.74-1.38 (overlapping m, 6H), 0.97 (s, 6H, 2x-CH_3 of Dde);

^{13}C-NMR ($CDCl_3$): δ [198.59, 196.83 (-CO- of Dde)], 175.19 (=C(CH_3)-NH), 173.14 (COO-Allyl), 131.60 (-CH=CH_2), 118.51 (-CH=CH_2), 107.56 (=C= of Dde), 65.33 (O-CH_2-CH=), 60.10 (-CH2- of Dde), 53.92, 42.96, 33.98, 29.83, 28.59, 28.02, 22.87, 17.65 (CH_3 of Dde).

EXAMPLE 17

***N*-(2-Boc-aminoethyl)- Lysine(Dde)-Allyl (17)**

Preparation: Procedure (b), yield= %65

MS (FAB) *m/z* 494 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 13.45 (s, 1H, -HN-Dde), 5.98-5.85 (10 line m, -CH=CH_2), 5.33 (dd, 1H, J_{trans}=17.29, 1.47 Hz), 5.28 (dd, 1H, J_{cis}=10.55, 1.17 Hz), 4.56 (dd, 5.86, 1.17Hz, O-CH_2-CH=), 3.4 (overlapping m, 3H, $^{\alpha}$CH, -CH_2-NH-Dde), 3.2 (m, 2H), 2.8 (m, 1H), 2.7 (m, 1H), 2.55 (s, 3H, -HN-C-CH_3), 2.36 (s, 4H, 2x-CH_2- of Dde), 1.8-1.5 (2 x m, 6H), 1.44 (s, 9H, boc), 1.03 (s, 6H, 2x-CH_3 of Dde); ^{13}C-NMR ($CDCl_3$): δ [198.79, 197.21 (-CO- of Dde)], 174.68 (=C(CH_3)-NH), 173.68 (COO-Allyl), 156.37 [-NH-COO-C($Me)_3$], 132.00 (-CH=CH_2), 119.27(-CH=CH_2), 108.08(=C= of Dde), 79.47 [COO-C($Me)_3$], 65.83 (O-CH_2-

CH=), 60.99 (-CH2- of Dde), 53.07, 47.83, 43.40, 40.55, 32.94, 30.35, [28.96, 28.68, 28.52, -COO-C($\underline{C}H_3)_3$], 23.35, 87, 18.18 (CH_3 of Dde).

C.H.N analyse for $C_{26}H_{43}N_3O_8$. H_2O: calc. C 61.03, H 8.86, N 8.21; found C 61.12, H 8.78, N 8.13.

EXAMPLE 18

***N*-(2-Boc-aminoethyl)-*N*-(Thymine-1-ylacetyl)-Lysine-N'-(Dde) *O*-Allyl (18)**

Preparation: Procedure (c), light yellow crystalline. Yield = 87%

Mp = 84-86; MS (FAB) *m/z* 660 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 13.4 (s, 1H, -HN-Dde), 9.56 (s, 1H, aromatic proton of Thymine), 6.99 (S, 1H, -NH- of Thymine), 5.97-5.84 (m, 1H, -$\underline{C}H=CH_2$), 5.66 (s, 1H, boc-NH-), 5.35 (dt,1H, J_{trans}=17.28, 1.46 Hz), 5.25 (dd, 1H, J_{cis}=10.55, 1.17 Hz), 4.7-4.4 (overlapping m and s, 4H, O-$C\underline{H}_2$-CH=, CO-$C\underline{H}_2$-Thymine), 4.2 (t, 1H), 3.7 (m, 1H), 3.44-3.27 (overlapping m, 5H), 2.55 (s, 3H, -HN-C-CH_3), 2.37 (s, 4H, 2 x-CH_2- of Dde), 2.05 (m, 4H), 1.89 (s, 3H, CH_3 of Thymine)1.7 (m, 2H), 1.45 (s, 9H, boc), 1.03 (s, 6H, 2x-CH_3 of Dde); ^{13}C-NMR ($CDCl_3$): δ = 197.81 (-CO- of Dde), 173.54, 170.33, 167.50, 163.94, 155.89 (-NH-COO), 150.74, 140.91, 131.26 (-$\underline{C}H=CH_2$), 119.26 (-CH=$\underline{C}H_2$), 110.41, 107.80 (=C= of Dde), 79.85 [-COO-$\underline{C}(Me)_3$], 66.25 (-$\underline{C}H_2$-CH=), 60.27 (-CH_2- of Dde), 52.69, 48.30, 47.66, 42.93, 39.11, 30.01, [28.31, 28.13, 28.01, -COO-C($\underline{C}H_3)_3$], 23.36, 17.89 (CH_3 of Dde), 12.29 (CH_3 of Thymine).

C.H.N analyse for $C_{33}H_{49}N_5O_9$: calc. C 60.08, H 7.49, N 10.61; found C 59.70, H 7.49, N 10.50.

EXAMPLE 19

***N*-(2-Boc-aminoethyl)-*N*-(Thymine-1-ylacetyl)-Lysine-*O*-Allyl (19)**

Preparation: 1.4 g (2.1 mmol) **18** was dissolved in a solution of 18 ml allyl alcohol and 2 ml hydrazin hydrate and stirred for 15 min. 200 ml DMF was added and the reaction mixture was evaporated under high vacuum. 50 ml Water was added to the remaining oil and extracted with diethylether (3 x 50 ml). The water phase was freeze dried and 0.8 g (1.6 mmol) titled compound was obtained as slightly yellow crystalline, which was used for the next step without further purification (yield = 76%). A sample of product was purified by HPLC and collected as TFA salt.

Mp = 81-83; MS (FAB) *m/z* 496 (M+H); ^{1}H-NMR, (CD_3OD): δ 7.34 (S, aromatic proton of Thymine), 6.03-5.94 (12 line m, 1H, -$\underline{C}H=CH_2$), 5.37(ddd,1H, J_{trans}=17.21, 3.11, 1.46 Hz), 5.27 (dd, 1H, J_{cis}=10.44, 2.56, 1.28 Hz), 4.8-4.6 (ddt, 2H, J=32, 5.67, 1.28 Hz, O-$C\underline{H}_2$-CH=), 4.78 (s, 2H, CO-$C\underline{H}_2$-Thymine), 4.37 (dd, 1H, J=8.8, 5.86 Hz, $^{\alpha}$CH), 3.7 (m, 1H, boc-HN-

CH2-CHH'-), 3.4 [overlapping m and d (J=0.74), 3H, boc-HN-CH_2-CHH'-, -NH_2), 3.23 (m, 1H), 3.03 (m, 1H), 3.97 (t, 2H, j=7.51, -CH_2-NH_2), 2.2-2 (dm, 2H, $^{\beta}CH_2$), 1.9 (s, 3H, CH_3 of Thymine) 1.7 (m, 2H), 1.49 [overlapping s and m, 11H, boc(9H), -CH_2-CH_2-NH_2]; ^{13}C-NMR (CD_3OD): (major rotamer) δ 171.79, 169.81, 166.98, 158.50 (-NH-COO-t-butyl), 153.12, 143.74, 133.44 (-CH=CH_2), 119.03 (-CH=CH_2), 116.38, 111.11, 80.74 [-COO-C(Me)$_3$], 67.21 (-CH_2-CH=), 61.94, 50.21, 40.61, 29.61, 28.81, 28.37, 27.83, 24.30, 12.32 (CH_3 of Thymine). C.H.N analyse for $C_{23}H_{37}N_5O_7$. 2 CF_3COOH: calc. C 44.82, H 5.43, N 9.68; found C 44.61, H 5.66, N 9.92.

EXAMPLE 20

_N_-boc-_N_-(Thymine-1-ylacetyl)Lysine-[_N-N_-bis(2,3,4,5-tetra-_O_-acetyl Galactose-1-yl)-ethyl]-_O_-Allyl (20)

Preparation: 300mg (0.6 mmol) **19** was dissolved in 10 ml methanol, 500 mg (1.33 mmol, 2.2 eq) **(M5)** was added and stirred for 10 min. 80 µml (1.3 mmol) Acetic acid and 0.6g (10 mmol) natrium cyanoborohydrate was added sequentially. After 15 min the same amounts of acetic acid and $NaCNBH_3$ were added and the reaction mixture was stirred for further 30 min at room temperature. Volatile was removed under vacuum and remaining dissolved in 100 ml ethylacetate and extracted with $NaHCO_3$ (2 x 50ml) saturated solution and 50 ml brine respectively. Organic phase was dried over magnesium sulphate and evaporated to dryness under vacuum. The residue was purified on silica gel column eluting ethylacetate-methanol 10:0 to 10:0.5. 440 mg (0.36 mmol) titled compound was obtained as white crystalline. Yield = 60%.

Mp = 106-108; MS (FAB) *m/z* 1212 (M+H); ^{1}H-NMR, ($CDCl_3$): resolved signals: δ 7 (s, 1H, aromatic proton of Thymine), 5.9 (m, 1H, -CH=CH_2), 5.5 (br.s, 1H, -NH-boc), 5.37 (d, 2H, J=2.74 Hz, 2x^{4}CH-sugar), 5.3 (dd, 1H, J_{trans}=17.2, 1.28 Hz), 5.2 (overlapping, 5H, -CH=CHH', 2x^{3}CH- and 2x^{2}CH- of sugar), 4.64 (s, 2H), 4.58 (d, 2H, J=5.86 Hz, O-CH_2-CH=), 4.29 (br.d, 2H, J=10.07), 4.15 (br., 2H), 4 (br.d 2H, J=8.4), 2.2-2 (4s, 24H, CO-CH_3 of sugar), 1.8 (s, 3H, CH_3 of Thymine), 1.4 (overlapping s, 11H, 9H of boc, 2H of lysine side chain); ^{13}C-NMR ($CDCl_3$): δ 170.75, 169.97, 169.65, 169.59, 167.58, 164.13, 156.00, 151.06, 141.38, 131.24, 119.06, 110.31, 79.65, 68.20, 67.44, 66.65, 66.18, 60.75, 60.18, 50.01, 39.12, 28.25, 20.66, 20.61, 20.48, 12.00.

HRMS $(M+H)^+$, calcd (found) for $C_{55}H_{82}N_5O_{25}$ are 1212.5299 (1212.5360).

EXAMPLE 21

***N*-boc-*N*-(Thymine-1-ylacetyl)Lysine-[*N*-*N*-bis(2,3,4-tri-*O*-acetyl Fucose-1-yl)-ethyl]-*O*-Allyl (21)**

Preparation: The Procedure is the same as described above for the synthesis of **20.** yield = 63%.

Mp = ; MS (FAB) *m/z* 1096 (M+H); ^{1}H-NMR, ($CDCl_3$): resolved signals: δ 7 (s, 1H, aromatic proton of Thymine), 5.9 (m, 1H, -CH=CH_2), 5.6 (br.s, 1H, -NH-boc), 5.3 (s, 1H), 5.2 (overlapping, 4H, -CH=CHH', sugar), 4.58 (s, 2H, O-CH_2-CH=), 4.2 (br.s, 1H), 4 (dd, 2H, J=7.3, 0.8 Hz), 3.4-3.2 (br. 2H), 2.9 (br.s, 1H), 2.8 (br.s, 1H), 2 (3s, 18H, CO-CH_3 of sugar), 1.8 (s, 3H, CH_3 of Thymine), 1.4 (s, 9H, boc), 1.2 (dd, 2H, J=7.3, 1.2 of lysine side chain), 1.1 (d, 6H, J=3.8, methyl group of fucose); ^{13}C-NMR ($CDCl_3$): δ 170.87, 170.45, 170.17, 169.95, 167.21, 164.46, 155.90, 151.11, 141.38, 131.18, 130.89, 119.34, 118.79, 110.26, 80.08, 72.51, 70.39, 69.75, 69.50, 68.07, 67.86, 66.05, 60.80, 60.08, 53.51, 50.20, 48.69, 48.01, 38.89, 36.44, 31.28, 28.09, 23.63, 21.65, 20.73, 20.60, 20.48, 20.38, 16.00, 15.47, 13.87, 11.94. HRMS $(M+H)^+$, calcd (found) for $C_{51}H_{78}N_5O_{21}$ are 1096.5189(1096.5192).

EXAMPLE 22

***N*-boc-*N*-(Thymine-1-ylacetyl)Lysine-[*N*-(2,3,4,5-tetra-*O*-acetyl Galactose-1-yl)-acetyl]-*O*-Allyl (22)**

1.03 g (2.64 mmol, 1.1 eq) **(M6)**, 470 mg (2.88 mmol, 1.2 eq) DhbtOH, and 740mg (3.6 mmol, 1.5 eq) DCC were mixed in 20 ml DMF and stirred for 30 min under Nitrogen. A solution of 1.2 g (2.4 mmol) **19** in 10 ml DMF was added and the reaction mixture was stirred for further 3h. Volatiles were removed under vacuum and the residue dissolved in 200ml ethylacetate. Insoluble DCU was filtered off and the filtrate was extracted with $NaHCO_3$ saturated solution (2 x 100 ml) and brine (100 ml) respectively. Organic phase was dried over magnesium sulphate and evaporated to dryness under vacuum. The remaining was purified on silica gel column eluting ethylacetate. 1.1 g (1.2 mmol) title compound was obtained as white crystalline. Yield = 61%.

Mp = 82-84; MS (FAB) *m/z* 868 (M+H); ^{1}H-NMR, ($CDCl_3$): resolved signals: δ 9.39 (aromatic proton of Thymine), 6.94 (s, 1H, -NH- of Thymine), 6.64 (s, 1H, -NH-CO-sugar), 5.92-5.85 (m, H, -CH=CH_2), 5.42 (overlapping d, 2H, J=2.75, ^{4}CH-sugar, -NH-boc), 5.32 (dd, 1H, J_{trans}=17.2, 1.46 Hz), 5.25 (overlapping, 3H, -CH=CHH', ^{3}CH- and ^{2}CH- of sugar), 4.7 (m, 1H), 4.6 (d, 2H, J=5.86), 4.5 (m, 1H), 4.3-4.1 (m, 5H), 3.6 (m, 1H), 3.35 (m, 3H), 3.2 (br., 2H), 2.6 (m, 1H), 2.45 (m, 1H), 2.15-2 (3s, 12H, CO-CH_3 of sugar), 1.9 (s, 3H, CH_3 of Thymine), 1.6 (br., 2H), 1.4 (overlapping s, 11H, 9H of boc, 2H of lysine side chain); ^{13}C-NMR ($CDCl_3$): δ 170.56, 169.85, 169.77, 169.44, 167.47, 163.93, 155.82, 151.40, 140.89, 131.23 (-

CH=CH_2), 119.09 (-CH=CH_2), 110.93, 79.86 [-O-C(Me)$_3$], 69.23, 68.87, 68.23, 67.60, 66.82, 66.12, 60.85, 59.64, 48.88, 47.13, 38.99, 38.59, 34.74, 28.28, 28.04, 27.58, 22.79, 20.61, 20.51, 12.20(CH_3 of Thymine)

C.H.N analyse for $C_{39}H_{57}N_5O_{17}$.1/2 H_2O: calc. C 53.42, H 6.67, N 7.99; found C 53.25, H 6.71, N 7.44.

EXAMPLE 23

_N_-boc-_N_-(Thymine-1-ylacetyl)Lysine-[_N_-(2,3,4,5-tetra-_O_-acetyl-Mannose-1-yl)-acetyl]-_O_-Allyl (23)

Preparation: The Procedure is the same as described above for the synthesis of **22.** Yield = 58%.

Mp = ; MS (FAB) *m/z* 868 (M+H); ^{1}H-NMR, ($CDCl_3$): resolved signals: δ 9.35 (aromatic proton of Thymine), 6.94 (s, 1H, -NH- of Thymine), 6.78 (s, 1H, -NH-CO-sugar), 5.8 (m, 1H, -CH=CH_2), 5.45 (s, 1H, -NH-boc), 5.35 (dd, 1H, J_{trans}=17, 1.2 Hz), 5.25 (m, 2H of sugar), 4.6 (d, 2H, J=5.5), 4.5 (s, 1H), 4.3 (dd, 1H, J=12.1, 5.7 Hz), 4.2 (dd, 1H, J= 12.1, 8.2), 4.1 (m, 1H), 3.6 (m, 1H), 3.35 (m, 5H), 2.6 (m, 2H), 2.15-2 (4s, 12H, CO-CH_3 of sugar), 1.9 (s, 3H, CH_3 of Thymine), 1.6 (br., 2H), 1.4 (overlapping s, 11H, 9H of boc, 2H of lysine side chain); ^{13}C-NMR ($CDCl_3$): δ 170.73, 170.19, 169.97, 169.48, 169.28, 167.36, 163.82, 156.56, 151.39, 143.55, 141.16, 131.21 (-CH=CH_2), 127.70, 127.01, 124.81, 119.93, 119.21 (-CH=CH_2), 110.87, 71.56, 70.33, 69.35, 68.11, 67.26, 66.67, 66.24, 61.73, 59.90, 47.06, 39.51, 38.79, 36.95, 28.14, 27.62, 22.85, 20.66, 12.18 (CH_3 of Thymine).

EXAMPLE 24

_N_-boc-_N_-(Thymine-1-ylacetyl)Lysine-[_N_-(2,3,4,5-tetra-_O_-acetyl fucose-1-yl)-acetyl]-_O_-Allyl (24)

Preparation: The Procedure is the same as described above for the synthesis of **22.** Yield = 65%.

Mp= ; MS (FAB) *m/z* 810 (M+H); ^{1}H-NMR, ($CDCl_3$): resolved signals: δ 9.64 (aromatic proton of Thymine), 6.94 (s, 1H, -NH- of Thymine), 6.88 (s, 1H, -NH-CO-sugar), 6-5.8 (m, H, -CH=CH_2), 5.5 (s, 1H, -NH-boc), 5.37 (d, 1H, J=3.8) 5.3 (overlapping, 2H, -CH=CHH'), 5.16 (m, 1H of sugar), 4.7 (d, 1H, J=15.5), 4.65 (m, 1H), 4.6 (d, 2H, J=5.8), 4.3 (m, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.8 (m, 1H), 3.5-3.1 (m, 5H), 2.9 (dd, 1H, J=23.1, 2.3Hz), 2.7 (m, 1H), 2.4-2.2 (m, 2H), 2.15-2 (3s, 9H, CO-CH_3 of sugar), 1.9 (s, 3H, CH_3 of Thymine), 1.4 (s, 9H of boc), 1.2 (m, 2H, of lysine side chain); ^{13}C-NMR ($CDCl_3$): δ 170.42, 169.95, 169.74, 169.68, 169.55, 167.13, 163.86, 162.37, 155.81, 151.53, 140.81, 131.25 (-CH=CH_2), 119.08 (-

CH=$\underline{C}H_2$), 111.01, 79.83 [-O-$\underline{C}$(Me)$_3$], 69.36, 68.43, 68.23, 67.95, 66.16, 61.64, 60.24, 48.95, 38.83, 37.41, 36.34, 35.68, 33.78, 28.72, 28.34, 27.33, 27.46, 24.80, 22.67, 20.91, 20.69, 20.62, 14.63, 14.05, 12.30 (CH_3 of Thymine).

EXAMPLE 25

***N*-Fmoc-*N*-(Thymine-1-ylacetyl)Lisine-[*N*-(2,3,4,5-tetra-*O*-acetyl Galactose-1-yl)-acetyl]-*O*-Allyl (25)**

Preparation: procedure (d). Yield = 91%.

Mp = 93-95; MS (FAB) *m/z* 990 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.33 (aromatic proton of Thymine), 7.6-7.1 (8H, florenyl aromatics), 6.64 (s, 1H, -NH- of Thymine), 6.51 (s, 1H, -NH-CO-sugar), 5.8-5.6 (overlapping m, 2H, -$\underline{C}$H=CH_2, -NH-fmoc), 5.27 (s, 1H, ^{4}CH-sugar), 5.15 (d, 1H, J_{trans}=16.66 Hz), 5.07 (overlapping, 3H, -CH=CH$\underline{H}$', ^{3}CH and ^{2}CH of sugar), 4.55 (br.d, 1H, J=3.84), 4.45 (d, 2H, J=5.86 Hz, O-$C\underline{H}_2$-CH=), 4.28 (overlapping s, 3H), 4.2 (d, 1H, J=7.14), 4.1-4 (m, 5H), 3.42 (m, 1H), 3.29-3.26 (overlapping s, 3H), 3.04 (br.s, 2H), 2.46 (dd, 1H, J=14.83, 9.15 Hz), 2.26 (m, 1H), 2-1.8 (4s, 12H, -CO-CH_3 of sugar), 1.68 (s, 3H, CH_3 of Thymine), 1.4 (m, 1H), 1.2 (m, 3H); ^{13}C-NMR ($CDCl_3$): δ 170.56, 170.46, 169.80, 169.72, 169.41, 169.36, 167.51, 163.98, 156.48, 151.29, 143.47, 143.44, 141.07, 131.18, 127.60, 127.49, 126.89, 124.71, 119.83, 119.03, 110.59, 77.41, 76.90, 76.39, 69.21, 68.75, 68.17, 67.64, 67.52, 66.73, 66.48, 66.06, 60.77, 59.54, 48.68, 46.97, 39.52, 38.62, 34.66, 28.16, 27.69, 22.87, 20.52, 20.43, 12.08.

HRMS $(M+H)^+$, calcd (found) for $C_{49}H_{60}N_5O_{17}$ are 990.3984(990.3940).

EXAMPLE 26

***N*-Fmoc-*N*-(Thymine-1-ylacetyl)Lysine-[*N*-(2,3,4,5-tetra-*O*-acetyl mannose-1-yl)-acetyl]-*O*-Allyl (26)**

Preparation: procedure (d). Yield = 88%.

Mp= ; MS (FAB) *m/z* 990 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.24 (aromatic proton of Thymine), 7.7-7.2 (8H, florenyl aromatics), 6.71 (overlapping-s, 2H, -NH- of Thymine, -NH-CO-sugar), 5.8 (overlapping-m, 2H, -$\underline{C}$H=CH_2, -NH-fmoc), 5.28 (s, 1H, sugar), 5.2(m, 2H, -CH=C$\underline{H}\underline{H}$'), 5.06 (t, 2H, J=6.7), 4.55 (d, 2H, J=4.1), 4.4 (3, 2H, O-$C\underline{H}_2$-CH=), 4.3 (m, 1H), 4.2 (m, 1H), 4.1 (m, 1H), 3.6 (m, 1H), 3.4-3.1 (m, 3H), 2.5 (m, 2H), 2 (s, 12H, -CO-CH_3 of sugar), 1.78 (s, 3H, CH_3 of Thymine), 1.5 (m, 1H), 1.2 (m, 3H); ^{13}C-NMR ($CDCl_3$): δ 170.72, 169.54, 165.72, 163.81, 151.40, 143.57, 141.17, 136.86, 131.22, 127.70, 127.01, 124.89, 119.93, 119.22, 110.10, 81.47, 67.27, 66.65, 66.24, 61.74, 47.07, 20.65, 20.43, 12.18.

HRMS $(M+H)^+$, calcd (found) for $C_{49}H_{60}N_5O_{17}$ are 990.3984(990.3987).

EXAMPLE 27

***N*-Fmoc-*N*-(Thymine-1-ylacetyl)Lysine-[*N*-(2,3,4-tri-*O*-acetyl fucose-1-yl)-acetyl]-*O*-Allyl (27)**

Preparation: procedure (d). Yield = 89% **3**

Mp= ; MS (FAB) *m/z* 932 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.85 (aromatic proton of Thymine), 7.7-7.2 (8H, florenyl aromatics), 7 (s, 1H, -NH- of Thymine), 6.8 (s, 1H, -NH-CO-sugar), 6 (s, 1H, -NH-fmoc), 5.9 (m, 1H, -CH=CH_2), 5.28 (s, 1H, sugar), 5.2 (m, 2H, -CH=CHH'), 5.1 (s, 1H), 4.6 (overlapping-s, 3H), 4.4 (m, 2H), 4.25 (br.s, 1H), 4.2(m, 1H), 2 (s, 9H, -CO-CH_3 of sugar), 1.8 (s, 3H, CH_3 of Thymine), 1.5-1.2 (m, 4H of Lysine side chain); ^{13}C-NMR ($CDCl_3$): δ 170.99, 170.46, 170.16, 169.98, 169.79, 169.62, 167.11, 163.90, 156.50, 151.60, 143.65, 143.31, 141.11, 131.22, 130.90, 127.65, 127.02, 126.96, 124.87, 119.88, 119.13, 110.87, 69.05, 68.19, 67.70, 66.60, 66.20, 61.55, 60.23, 48.77, 46.99, 39.32, 37.69, 35.20, 28.77, 27.46, 22.74, 20.89, 20.61, 20.56, 20.47, 14.72, 14.02, 12.15.

HRMS $(M+H)^+$, calcd (found) for $C_{47}H_{58}N_5O_{15}$ are 932.3929(932.3945).

EXAMPLE 28

***N*-(2-Fmoc-aminoethyl)- Asp(tBu)-Allyl (30)**

To 4.5 g (10 mmol) **28** [prepared by procedure (a)] was added 50 ml of a solution of 20% piperidine in DCM. After 30 min, 100 ml toluene was added and volatile were removed under vacuum. The residue was purified with a short silica gel column eluting ethylacetate-methanole 10:0 to 10:1. 1.8 g (7.9 mmol) **29** was obtained as slightly yellow oil. This oil was used for *procedure (b).* 1.7 g (3.4 mmol) title compound was obtained as colourless oil. Overall yield = 34%.

$[\alpha]_D^{22}$= (*c*=1, methanol); MS (FAB) *m/z* 495 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 7.7-7.2 (8H, Florenyl aromatic protons), 5.96-5.84 (16 line m, 1H, -CH=CH_2), 5.56 (br.s, 1H, fmoc-HN-), 5.35 (dt, 1H, J_{trans}=15.9, 1.46 Hz), 5.25 (dt, 1H, J_{cis}=10.5, 1.28Hz), 4.6 (dd, 2H, J=5.9, 1.1 Hz, O-CH_2-CH=), 4.4 (d, 2H, J=7 Hz), 4.2 (t, 1H, J=7 Hz), 3.6(t, 1H, J=7.3 Hz, $^{\alpha}$CH), 3.3 (m, 2H, $^{\beta}$CH), 2.9 (m, 1H), 2.7 (m, 2H), 2.6 (m, 1H), 2.3 (br.s, 1H), 1.4 (s, 9H, *t*-butyl) ^{13}C-NMR ($CDCl_3$): δ 173.02 (COO-Allyl), 169.89, 156.37, 143.84, 141.06, 131.47(-CH=CH_2), 127.41, 126.81, 124.95, 119,71, 118.68(-CH=CH_2), 81.17[-O-C(Me)$_3$], 66.5 (-CH_2-CH=), 65.62 (β carbon), 57.12 (α carbon), 47.05, 40.34, 38.97, 27.85 [-COO-C(CH_3)$_3$].

HRMS $(M+H)^+$, calcd (found) for $C_{28}H_{35}N_2O_6$ are 495.2495(495.2480).

EXAMPLE 29

N-(2-fmoc-aminoethyl)-N-(Thymine-1-ylacetyl)-Asp-(tBu)-O-Allyl (31)

Preparation: procedure (c). Yield = 81%.

Mp= ; $[\alpha]_D^{22}$= (c=0.25, methanol); MS (FAB) *m/z* 661 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.15 (s, 1H,Thymine aromatic), 7.75-7.26 (8H, Florenyl aromatic protons), 6.75 (s, 1H, Thymine-NH-), 5.9 (s, 1H, fmoc-HN-), 5.8 (m, 1H, -C<u>H</u>=CH_2), 5.3 (d, 1H, J_{trans}=17.3 Hz), 5.2 (d, 1H, J_{cis}=10.5 Hz), 4.6 (m, 3H, O-C<u>H_2</u>-CH=, °CH), 4.45 (s, 2H, -CO-CH2-Thymine), 4.2-4.1 (m, 3H), 3.4-3.4 (m, 2H), 3.4-3.2 (m, 2H), 2.9-2.7(m, 2H), 1.8 (s, 3H, Thymine-CH_3), 1.4 (s, 9H, -COOtBu); ^{13}C-NMR ($CDCl_3$): δ 170.49, 169.36, 167.05, 164.06, 156.52, 150.62, 143,63, 143.52, 141.09, 140.85, 131.10(-<u>C</u>H=CH_2), [(130.71, 127.57, 126.92, 124.83, 119.79(florenyl)], 119.24(-CH=<u>C</u>H_2), 110.32, 82.27, 81.41, 66.84, 66.51, 60.24(-<u>C</u>H_2-CH=), 58.08, 48.85, 47.82, 47.10, 39.15, 35.41, 27.85, 14.04, 12.19(Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{35}H_{41}N_4O_9$ are 661.2874(661.2881).

EXAMPLE 30

N-(2-fmoc-aminoethyl)-N-(Thymine-1-ylacetyl)-Asp-O-Allyl (32)

Preparation: To 3.3 g (5 mmol) **31** was added a solution of 95% TFA 5% TES. The reaction mixture was stirred until total conversion of starting material according to TLC. TFA solution was co-evaporated with DCM under vacuum. Titled compound was obtained as slightly yellow crystalline which was used for the next step without further purification (Yield = 62%); Mp = $[\alpha]_D^{22}$= (c=0.25, methanol); MS (FAB)=605 *m/z* (M+H); ^{1}H-NMR, (DMSO): δ 11.3 (s, 1H,Thymine aromatic), 7.91-7.22 (8H, Florenyl aromatic protons, 1H, Thymine-NH-), 5.8 (m, 1H, -C<u>H</u>=CH_2), 5.3 (dd, 1H, J_{trans}=17.3, 1.76 Hz), 5.1 (dd, 1H, J_{cis}=10.55, 1.47 Hz), 4.6 (d, 2H, J=7 Hz, O-C<u>H_2</u>-CH=), 4.5 (s, 2H, -CO-CH2-Thymine), 4.4 (t, 1H, J=6.4, °CH), 4.3 (d, 2H, J=6.8, florenyl-C<u>H</u>2-O-), 4.2 (t, 1H, J=6.8, florenyl=C<u>H</u>-CH2-O-), 3.5 (m, 2H), 3.4 (m, 2H), 3.2 (dd, 2H, J=17, 7.3 Hz), 1.7 (s, 3H, Thymine-CH_3); ^{13}C-NMR (CD_3OD): δ 174.50, 170.90, 169.54, 166.94, 158.90, 152.80, 145.30, 143,64, 142.57, 142.16, 133.25, 131.09 (-<u>C</u>H=CH_2), [(130.44, 128.83, 128.21, 127.13, 126.20, 121.00(florenyl)], 118.96 (-CH=<u>C</u>H_2), 110.89, 67.80, 67.38, 61.59, 59.96(-<u>C</u>H_2-CH=), 40.47, 35.32, 14.53, 12.34 (Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{31}H_{33}N_4O_9$ are 605.2224(605.2248).

EXAMPLE 31

fmoc-N-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-O-acetyl Galactose-1-yl)-amide]-O-Allyl (33)

Preparation: procedure (e). Yield = 64%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 934 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.5 (s, 1H,Thymine aromatic), 7.7-7.2 (m, 8H, Florenyl aromatic protons), 6.6 (s, 1H, Thymine-NH-), 5.9 (overlapping m, 2H, -C<u>H</u>=CH_2, fmoc-HN-), 5.3 (d, 1H, J=1.6Hz), 5.25-5.15 (m, 3H), 5.05 (d, 2H, J=5.3 Hz), 4.6 (m, 2H), 4.4 (m, 2H), 4.1 (m, 1H), 4 (m, 3H), 3.6-3.2 (m, 5H), 2.8 (m, 1H), 2.1-1.9 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ^{13}C-NMR ($CDCl_3$): δ 171.21, 170.22, 169.84, 169.76, 169.58, 166.56, 164.17, 156.81, 156.57, 151.39, 143.68, 143.45, 141.17, 140.94, 131.20(-<u>C</u>H=CH_2), 127.71, 127.04, 124.89, 119.92, 119.16 (-CH=<u>C</u>H_2), 110.60, 80.39, 78.26, 72.13, 71.36, 67.86, 67.19, 66.81, 66.55, 61.44, 61.06, 57.81, 49.22, 48.92, 48.77, 47.16, 39.19, 36.00, 33.69, 25.47, 24.79, 20.71, 20.61, 20.57, 20.46 (sugar-CO-<u>C</u>H_3 groups), 12.26 (Thymine-CH_3).

C.H.N analyse for $C_{45}H_{51}N_5O_{17}$, H_2O: calc. C 56.78, H 5.61, N 7.36; found C 56.87, H 5.94, N 7.57.

EXAMPLE 32

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-*O*-acetyl mannose-1-yl)-amide]-*O*-Allyl (34)

Preparation: procedure (e). Yield = 60%.

Mp= ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 934(M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.5 (s, 1H,Thymine aromatic), 7.7-7.2 (m, 8H, Florenyl aromatic protons), 6.7 (s, 1H, Thymine-NH-), 6 (br.s, 1H, fmoc-HN-), 5.9 (m, 1H, -C<u>H</u>=CH_2), 5.5 (d, 1H, J=8.8Hz), 5.4 (d, 1H, , J=8.8 Hz), 5.3-5 (m, 5H), 4.6 (m, 2H), 4.4 (m, 2H), 4.2 (m, 3H), 4.1 (m, 2H), 3.8-3.4 (m, 5H), 3.1 (m, 1H), 2.9 (m, 1H), 2.2-1.9 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ^{13}C-NMR ($CDCl_3$). Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 934 (M+H); ^{1}H-NMR, ($CDCl_3$ ^{13}C-NMR ($CDCl_3$): δ 171.13, 170.95, 170.49, 170.30, 169.93, 169.85, 164.62, 157.14, 156.95, 151.54, 144.08, 141.49, 131.57(-<u>C</u>H=CH_2), 128.04, 127.35, 125.24, 120.27, 119.56 (-CH=<u>C</u>H_2), 110.77, 74.43, 71.83, 69.87, 67.00, 66.87, 66.05, 65.62, 62.61, 58.53, 49.56, 49.34, 47.44, 39.47, 34.13, 25.83, 25.16, 21.21, 21.01, 20.95, 20.84 (sugar-CO-<u>C</u>H_3 groups), 12.05 (Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{45}H_{52}N_5O_{17}$ is 934.3358 (934.3342).

EXAMPLE 33

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4-tri-*O*-acetyl fucose-1-yl)-amide]-*O*-Allyl (35)

Preparation: procedure (e). Yield = 77%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 876 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.1 (s, 1H,Thymine aromatic), 7.7-7.2 (m, 8H, Florenyl aromatic protons), 6.7 (s, 1H, Thymine-NH-),

5.9 (br.s, 1H, fmoc-HN-), 5.8 (m, 1H, -CH=CH_2), 5.3(s, 1H), 5.25 (s, 2H), 5.2 (m, 2H), 5 (m, 2H), 4.6 (m, 2H), 4.4 (m, 2H), 4.2-4 (m, 2H), 3.8 (d, 1H, J=6.4 Hz), 3.7 (q, 1H, J=6.4 Hz),3.4 (m, 2H), 3 (m, 1H), 2.9 (m, 1H), 2.2-2 (3s, 9H, sugar acetyl protons), 1.9 (s, 3H, Thymine-CH_3), 1.1 (s, 3H, fucose-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{44}H_{50}N_5O_{15}$ is 876.3303(876.3304).

EXAMPLE 34

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-*O*-acetyl glucosamine-1-yl)-amide]-*O*-Allyl (36)

Preparation: procedure (e). Yield = 73%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 933 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 10 (s, 1H,Thymine aromatic), 7.7-7.2 (m, 8H, Florenyl aromatic protons), 6.8 (s, 1H, Thymine-NH-), 6 (br.s, 1H, fmoc-HN-), 5.8 (m, 1H, -CH=CH_2) , 5.4-5 (m, 5H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (m, 2H), 4.2 (m, 3H), 4.1 (m, 3H), 3.8-3.2 (m, 6H), 2.1-2 (4s, 12H, sugar acetyl protons), 1.9 (s, 3H, Thymine-CH3); ^{13}C-NMR ($CDCl_3$): δ 171.78, 171.08, 170.97, 170.71, 170.51, 169.42, 169.23, 166.94, 164.52, 156.47, 151.12, 143.58, 141.06, 131.05, 130.79 (-CH=CH_2), 127.60, 126.92, 124.82, 119.84, 119.51, 119.17 (-CH=CH_2), 110.40, 79.39, 73.07, 67.89, 66.48, 61.68, 57.94, 52.75, 48.96, 48.28, 47.00, 39.14, 35.51, 33.67, 24.73, 22.74, 20.54, 20.43, (sugar-CO-CH_3 groups), 12.11 (Thymine-CH_3).

C.H.N analyse for $C_{45}H_{62}N_6O_{16}$, 3/2 H_2O: calc. C 56.30, H 5.78, N 8.75; found C 56.43, H 5.70, N 8.72.

EXAMPLE 35

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-*O*-acetyl galactosamine-1-yl)-amide]-*O*-Allyl (37)

Preparation: procedure (e). Yield = 60%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 933 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 10.2 (s, 1H,Thymine aromatic), 7.9-7 (m, 8H, Florenyl aromatic protons), 6.8 (s, 1H, Thymine-NH-), 6.3 (m, 1H), 6.1 (br.s, 1H, fmoc-HN-), 5.8 (m, 1H, -CH=CH_2) , 5.4-5.1 (m, 4H), 4.7 (m, 2H), 4.4 (m, 2H), 4.2 (m, 5H), 3.6-3.3 (m, 4H), 2.8 (m, 4H), 2.1-2 (m, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH3); ^{13}C-NMR ($CDCl_3$): δ 171.78, 171.08, 170.97, 170.71, 170.51, 169.42, 169.23, ^{13}C-NMR ($CDCl_3$): δ 172.32, 170.82, 170.54, 170.33, 170.04, 169.55, 169.37, 167.03, 164.53, 156.62, 151.35, 143.55, 141.04, 131.09, 127.59, 126.91, 124.80, 119.82, 119.07(-CH=CH_2), 110.41, 79.57, 71.83, 70.46, 67.91, 67.37, 66.86, 66.70, 66.45,

61.77, 61.31, 58.59, 49.20, 48.98, 47.96, 47.01, 39.18, 23.04, 22.95, 22.77, 20.52 (sugar-CO-$\underline{C}H_3$ groups), 12.04 (Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{45}H_{53}N_6O_{16}$ is 933.3518(933.3549).

EXAMPLE 36

4-C-(2,3,4,6-tera-O-acetyl-galactose-1-yl)-2-Z-amino-2-butenoic acid t-butyl ester (41)

Preparation: 2.2 g (5.8 mmol, 1.1 eq) **40** was dissolved in 20 ml dry THF. 0.8 ml (mmol, 1.1 eq) tetramethylguanidine was added at (–78°C) and stirred for 5 min. 1.9 g (5.27 mmol, 1 eq) 2,3,4,5 tetraacetyl galactose-1yl-acetaldehyde was added in 10 ml dry THF solution. The reaction mixture was allowed to reach the room temperature. Volatile was evaporated and the residue was purified on silica gel column eluting hexane-ethylacetate 1:1 solution. 2.2 g (3.5 mmol) titled compound was obtained as colourless oil. Yield = 66%.

Mp: ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 622 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 7.4 (m, 4H of cbz aromatic protons), 6.5 (overlapping, 2H, cbz-ring-^{4}CH-, cbz-HN-), 5.4 (t, 1H, J=3 Hz), 5.2 (dd, 1H, J=9.1, 4.8 Hz), 5.18 (dd, 1H, J=9.1, 3.3 Hz), 5.15 (d, 2H, J=1.3 Hz), 4.35 (m, 1H), 4.45 (m, 1H), 4.1-4 (m, 2H), 2.6 (m, 1H), 2.4 (m, 1H), 2.18 (d, 1H, J=8.4), 2.15-2 (4s, 12H, sugar acetyl protons), 1.4 (s, 9H, t-Bu); ^{13}C-NMR ($CDCl_3$): δ 170.42, 169.86, 169.68, 163.08, 153.86, 135.81, 129.60, 128.43, 128.16, 128.06, 82.06, 74.04, 71.02, 68.91, 68.51, 67.72, 67.55, 67.32, 67.25, 61.18, 27.87, 25.82, 20.62, 20.54.

HRMS $(M+H)^+$, calcd (found) for $C_{30}H_{40}NO_{13}$ is 622.2500(622.2495).

EXAMPLE 37

4-C-(2,3,4,6-tera-O-acetyl-galactose-1-yl)-2(2-fmoc-aminoethyl)-aminobutanoic acid t-butyl ester (43)

Preparation: 2.2 g (3.5 mmol) **41** was dissolved in 10 ml methanole. 50 mg Pd/C catalyst was added and the mixture hydrogenated at 1 atm for 3 hours. The catalyst was filtered off over celite and methanol was removed under vacuum. The remaining oil **42** was directly used for *procedure (b).* 2.1g (2.78 mmol) titled compound was obtained as white solid. Yield = 82%.

Mp = ; $[\alpha]_D^{22}$= (c=0.5, methanol); MS (FAB) *m/z* 755 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 7.7-7.2 (m, 8H, fmoc aromatic protons), 5.5 (overlapping s, 2H), 5.2 (m, 2H), 4.4 (d, 2H, 7 Hz), 4.2 (s, 2H), 4.1 (m, 2H), 3.3-3 (m, 4H), 2.8 (m, 1H), 2.6 (m, 1H), 2.2-2 (4s, 12H, sugar acetyl protons), 1.4(s, 9H, t-Bu); $CDCl_3$ ^{13}C-NMR ($CDCl_3$): δ 174.13, 170.53, 170.47, 170.40, 170.01, 169.93, 169.86, 169.76, 169.71, 16963, 156.37, 143.79, 143.69, 141.07, 127.45, 126.82, 124.90, 119.75, 81.43, 71.60, 68.26, 68.20, 68.00, 67.80, 67.71, 67.58, 67.44, 67.35, 66.51,

61.42, 61.24, 61.07, 61.00, 60.19, 47.33, 47.05, 28.79, 27.89, 27.47, 21.75, 20.86, 20.59, 20.53, 20.46 (sugar-CO-CH3 groups), 14.01.

HRMS $(M+H)^+$, calcd (found) for $C_{39}H_{51}N_2O_{13}$ is 755.3391 (755.3371).

EXAMPLE 38

4-C-(2,3,4,6-tera-O-acetyl-galactose-1-yl)-2[N,N(2-fmoc-aminoethyl)-(thymine-1-yl-methyl-carbonyl)-aminobutanoic acid t-butyl ester (44)

Preparation: procedure (c). Yield = 66%.

Mp: ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 951 (M+H); ^{1}H-NMR, ($CDCl_3$): δ 9.2 (s, 1H, thymine aromatic), 7.8-7.3 (m, 8H, fmoc aromatic), 6.9 (s, 1H, thymine-NH-), 5.8 (s, 1H, fmoc-HN-), 5.4 (s, 1H), 5.35 (dd, 1H, J=10.2, 3.3 Hz), 5.25 (dd, 1H, J=10.2, 5.7 Hz), 5.2 (d, 1H, J=3 Hz), 4.4 (m, 3H), 4.2-4 (m, 5H), 3.6-3.3 (m, 4H), 2.2-2 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, thymine-methyl), 1.4 (s, 9H, t-Bu); ^{13}C-NMR ($CDCl_3$): δ 170.46, 169.94, 169.84, 169.07, 168.19, 166.85, 163.99, 156.44, 150.82, 143.54, 141.08, 127.59, 126.89, 124.78, 119.83, 110.23, 82.49, 72.31, 71.83, 67.49, 66.93, 66.61, 61.81, 61.29, 60.20, 59.30, 48.87, 48.40, 47.89, 46.96, 46.10, 39.98, 39.38, 33.72, 27.75, 25.41, 24.88, 22.60, 21.16, 20.86, 20.68, 20.55, 14.01, 12.16.

HRMS $(M+H)^+$, calcd (found) for $C_{46}H_{57}N_4O_{16}$ is 921.3770(921.3782).

EXAMPLE 39

***N*-Fmoc-*N*-(Thymine-1-ylacetyl)Serine(2,3,4,5-tetra-*O*-acetyl-α-D-Galactose-1-yl)-COOH (1s)**

Preparation: procedure (f). Yield = 86%.

Mp = 124-127; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 867 (M+H); ^{1}H-NMR, (CD_3OD): characteristic signals: δ = 7.8-7.3 [m, 9H, (8H, Florenyl aromatic protons, 1H, Thymine aromatic)], 5.4 (s, 1H, sugar ^{4}CH), 5.15 (m, 2H, sugar ^{3}CH and ^{2}CH), 4.65 (overlapping s, 3H, sugar ^{1}CH, -CO-CH_2-Thymine), 2.2-2 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ^{13}C-NMR (CD_3OD): δ 170.20, 170.13, 170.05, 169.75, 165.15, 143.56, 143.46, 141.98, 140.73, 133.95, 128.16, 127.99, 126.92, 126.36, 126.30, 124.40, 124.30, 119.06, 108.83, 100.26 (sugar C1), 70.33, 70.13, 68.53, 68.44, 66.90, 65.86, 60.58, 47.95, 38.61, 18.88, 18.68, 18.59, 10.36.

HRMS $(M+H)^+$, calcd (found) for $C_{41}H_{47}N_4O_{17}$ is 867.2936 (867.2924).

EXAMPLE 40

***N*-Fmoc-*N*-(Thymine-1-ylacetyl)Threonine(2,3,4,5-tetra-*O*-acetyl-α-D-Galactose-1-yl)-COOH (2s)**

Preparation: procedure (f). Yield = 90%.

Mp = 128-131; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 881 (M+H); ^{1}H-NMR, (CD_3OD): characteristic signals: δ = 7.84-7.32 []m, 9H, (8H, Florenyl aromatic protons, 1H, Thymine aromatic), 5.41 (d, 1H, J=3.3 Hz, sugar ^{4}CH), 5.2 (dd, 1H, J=10.44, 3.3 Hz, sugar ^{3}CH), 5.1 (dd, 1H, $J_{1,2}$=7.5, $J_{2,3}$=10.5, sugar ^{2}CH), 2.18-2 (4s, 12H, sugar acetyl protons), 1.9 (s, 3H, Thymine-CH_3), 1.36 (d, 3H, J=5.86 Hz, ^{D}C-CH3); ^{13}C-NMR (CD_3OD): δ = 172.06, 171.51, 167.09, 145.38, 143.86, 142.61, 128.87, 128.26, 126.26, 121.03, 116.69, 110.78, 100.40(sugar C1), 74.76, 72.31, 71.97, 70.66, 68.80, 67.78, 62.69, 62.49, 20.93, 20.73, 20.62, 12.41.

HRMS $(M+H)^+$, calcd (found) for $C_{42}H_{49}N_4O_{17}$ is 881.3043 (881.3073).

EXAMPLE 41

***N*-boc-*N*-(Thymine-1-ylacetyl)Lisine-[*N*-*N*-bis(2,3,4,5-tetra-*O*-acetyl Galactose-1-yl)-ethyl]-OH (3s)**

Preparation: procedure (f). Yield = 80%.

Mp = 118-120; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 1172 (M+H); ^{1}H-NMR, (CD_3OH): resolved signals: δ 7.4 (s, 1H, aromatic proton of Thymine), 5.45 (d, 2H, J=2.74 Hz, 2 x ^{4}CH-sugar), 5.31 (dd, 2H, J=9.16, 3.3 Hz, 2 x ^{3}CH-sugar), 5.25 (m, 2H, 2 x ^{2}CH-sugar), 4.38 (m, 4H), 4.25 (m, 2H), 4.15 (m, 3H), 3.95 (dd, 1H, J=12.82, 3.66Hz), 3.65 (dt, 1H, J=2.38, 12.45 Hz), 3.5 (m, 2H), 3.15 (d, 2H, J=13.7 Hz), 2.9 (br, 2H), 2.8(m, 2H), 2.2-2 (4s, 24H, CO-CH_3 of sugar), 1.9 (s, 3H, CH_3 of Thymine), 1.8-1.6 (br. 4H), 1.47 (overlapping s, 11H, 9H of boc, 2H of lysine side chain); ^{13}C-NMR (CD_3OH): δ 172.41, 172.23, 171.91, 171.72, 171.69, 171.50, 170.39, 169.75, 167.08, 158.28, 153.16, 144.45, 144.16, 110.77, 110.57, 80.42, 71.31, 71.24, 70.29, 69.86, 69.78, 69.37, 69.20, 69.07, 66.30, 65.76, 62.88, 62.70, 54.96, 51.67, 50.87, 45.10, 40.60, 39.83, 32.81, 31.39, 30.56, 28.95, 28.88, 26.81, 26.26, 25.95, 25.66, 23.46, 23.01, 20.99, 20.79, 20.68, 12.43.

HRMS $(M+H)^+$, calcd (found) for $C_{52}H_{78}N_5O_{25}$ is 1172.4986 (1172.5027).

EXAMPLE 42

***N*-boc-*N*-(Thymine-1-ylacetyl)Lisine-[*N*-*N*-bis(2,3,4-tri-*O*-acetyl fucose-1-yl)-ethyl]-OH (4s)**

Preparation: procedure (f). Yield = 88%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 1056 (M+H);^{13}C-NMR (CD_3OH): δ 172.19, 171.65, 166.98, 162.58, 158.30, 153.14, 144.9, 133.86, 133.18, 133.05, 130.66, 130.13, 128.83, 128.35, 123.36, 114.36, 110.83, 108.98, 80.44, 80.08, 71.82, 71.51, 69.82, 69.34, 67.49, 62.40, 54.33, 51.85, 51.32, 50.66, 45.12, 40.60, 39.81, 30.22, 28.97, 28.90, 25.24, 22.13, 21.02, 20.83, 20.67, 16.43, 12.49, 11.99.

HRMS $(M+H)^+$, calcd (found) for $C_{48}H_{74}N_5O_{21}$ is 1056.4876(1056.4886).

***N*-boc-*N*-(Thymine-1-ylacetyl)Lisine-[*N*-(2,3,4,5-tetra-*O*-acetyl Galactose-1-yl)-acetyl]-OH (5s)**

Preparation: procedure (f). Yield = 95%.

Mp = 115-118; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 828 (M+H); ^{1}H-NMR, (CD_3OD): resolved signals: δ 7.37 (s, 1H, aromatic proton of Thymine), 5.44 (d, 1H, J=2.56 Hz, ^{4}CH-sugar), 5.3 (overlapping, 2H, ^{3}CH- and ^{2}CH-sugar), 4.7 (m, 2H), 4.5(m, 1H), 4.25 (m, 1H), 4.1 (m, 3H), 3.5 (m, 1H), 3.25 (m, 2H), 2.7 (m, 1H), 2.5 (dd, 1H, J=5.3, 2.2 Hz), 2.2-2 (4s, 12H, CO-CH_3 of sugar), 1.9 (s, 3H, CH_3 of Thymine), 1.6 (br. 2H), 1.4 (overlapping s, 11H, 9H of boc, 2H of lysine side chain); ^{13}C-NMR (CD_3OD): δ 173.13, 172.16, 170.41-169.52 (sugar-O-CO-Me), 167.69, 164.97 (-$\underline{C}$O-CH_2-Thymine), 156.48 (-NH-COO-t-butyl), 151.46, 141.90, 109.37, 78.68 [-O-$\underline{C}$(Me)$_3$], 74.39 (sugar C5), 69.32-66.93 (sugar C1-4), 60.52 (sugar C6), 48.68 (lysine, α carbon), 40.93, 38.31, 37.08, 33.06, 29.22-25.82 [-COO-C($\underline{C}H_3$)$_3$], 22.94-18.65 (sugar-O-CO-$\underline{C}H_3$), 10.34 (Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{38}H_{54}N_5O_{17}$ is 828.3515 (828.3515).

EXAMPLE 43

***N*-fmoc-*N*-(Thymine-1-ylacetyl)Lisine-[*N*-(2,3,4,5-tetra-*O*-acetyl Galactose-1-yl)-acetyl]-OH (6s)**

Preparation: procedure (f). Yield = 83%.

Mp = 130-132; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 951 (M+H); ^{1}H-NMR, (CD_3OH): resolved signals: δ 7.8-7.3 (9H, aromatic proton of Thymine, 8H of florenyl aromatics), 5.43 (d, 1H, J=2.4 Hz, ^{4}CH-sugar), 5.3 (overlapping, 2H, ^{3}CH- and ^{2}CH-sugar), 4.72 (m, 3H), 4.45 (d, 1H, J=6.6), 4.4 (m, 2H), 4.3-4.2 (m, 3H), 4.2-4.1 (m, 3H), 3.6 (m, 1H), 3.45 (m, 2H), 3.2 (m, 3H), 2.7 (dd, 1H, J=14.65, 9.34 Hz), 2.5 (dd, 1H, J=14.65, 5.31Hz), 2.2-2 (3s, 12H, CO-CH_3 of sugar), 1.9 (s, 3H, CH_3 of Thymine), 1.6 (br. 3H), 1.2 (m, 1H); ^{13}C-NMR (CD_3OH): δ 174.33, 172.23, 172.20, 171.89, 171.56, 171.41, 170.43, 169.78, 166.98, 158.89, 153.02, 145.02, 143.91, 142.67, 128.88, 128.23, 126.22, 121.04, 110.92, 71.28, 70.14, 69.41, 69.15,

69.00, 67.81, 62.52, 61.65, 50.20, 40.80, 40.30, 35.08, 30.12, 29.78, 24.96, 20.83, 20.76, 20.72, 20.62, 12.37(Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{46}H_{56}N_5O_{17}$ is 950.3671 (950.3666).

EXAMPLE 44

_N_-fmoc-_N_-(Thymine-1-ylacetyl)Lysine-[_N_-(2,3,4,5-tetra-_O_-acetyl mannose-1-yl)-acetyl]-_OH_ (7s)

Preparation: procedure (f). Yield = 92%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 951 (M+H); ^{13}C-NMR ($CDCl_3$): δ 193.55, 178.08, 172.71, 172.46, 171.75, 171.56, 171.44, 166.88, 153.09, 145.27, 144.01, 142.58, 130.33, 128.89, 128.24, 126.23, 121.04, 116.26, 110.95, 73.18, 72.40, 72.30, 71.40, 70.19, 68.28, 67.88, 63.44, 62.41, 40.15, 37.31, 30.17, 25.05, 20.87, 20.71(acetyl groups on sugar), 12.40 (CH_3 of Thymine)

EXAMPLE 45

_N_-fmoc-_N_-(Thymine-1-ylacetyl)Lysine-[_N_-(2,3,4-ttrl-_O_-acetyl fucose-1-yl)-acetyl]-_OH_ (8s)

Preparation: procedure (f). Yield = 86%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 892 (M+H); ^{1}H-NMR, (CD_3OD): resolved protons δ 7.8-7.2 (m, 8H, Florenyl aromatic protons), 6.9 (s, 1H, Thymine-NH-), 5.3 (overlapping s, 2H), 4.7 (s, 2H, -CO-CH_2-Thymine), 4.44 (d, 1H, J=6.6Hz), 4.38 (m, 1H), 4.25 (m, 1H), 4.15 (m, 1H), 3.6-3.2 (multiplets, 5H), 2.7 (m, 1H), 2.5 (m, 1H), 2.2-2 (3s, 9H, sugar acetyl protons), 1.85 (s, 3H, Thymine-CH_3), 1.6-1.3 (m, 4H, lysine side chain protons), 1.1 (d, 3H, J=4.2, fucose-CH_3); ^{13}C-NMR (CD_3OD): δ 174.67, 172.51, 172.24, 171.51, 170.32, 169.68, 166.93, 158.86, 152.99, 145.29, 143.93, 142.62, 133.19, 131.77, 130.48, 129.92, 128.89, 128.24, 126.22, 121.83, 121.05, 117.01, 110.89, 72.044, 71.53, 69.88, 69.00, 67.81, 61.93, 42.08, 40.75, 40.12, 34.79, 30.15, 29.75, 26.77, 26.09, 24.91, 20.80, 20.59, 16.50, 12.38.

HRMS $(M+H)^+$, calcd (found) for $C_{44}H_{54}N_5O_{15}$ is 892.3616(892.3635).

EXAMPLE 46

fmoc-_N_-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-_O_-acetyl Galactose-1-yl)-amide]-OH (9s)

Preparation: procedure (f). Yield = 94%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 894 (M+H); ^{1}H-NMR, (CD_3OD): resolved protons δ 7.8-7.3 (m, 8H, Florenyl aromatic protons), 7.2 (s, 1H, Thymine-NH-), 5.45 (s, 1H, sugar ^{4}CH), 5.37 (d, 1H, J=8.5 Hz, ^{2}CH), 4.24(m, 2H), 5.23 (d, 1H, J=13.4 Hz), 4.48 (t, 1H, J=6 Hz), 4.42 (d, 1H, J=3.3 Hz, -CO-CH_2-Thymine), 4.3-4.1 (m, 3H), 2.2-2 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ^{13}C-NMR (CD_3OD): δ 173.62, 172.93, 172.00, 171.79, 171.53, 169.34, 166.98, 158.89, 152.90, 145.33, 143.68, 142.64, 133.85, 133.21, 130.14, 128.89, 128.27, 126.29, 121.06, 110.93, 79.30, 73.41, 73.09, 69.81, 69.03, 68.36, 62.72, 59.72, 40.46, 37.15, 34.80, 32.77, 30.19, 26.79, 26.10, 24.91, 23.73, 20.94, 20.70, 20.64, 14.51, 12.38.

HRMS $(M+H)^+$, calcd (found) for $C_{42}H_{48}N_5O_{17}$ is 894.3045 (894.3072).

EXAMPLE 47

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-*O*-acetyl mannose-1-yl)-amide]-*OH* (10s)

Preparation: procedure (f). Yield = 95%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 894 (M+H); ^{1}H-NMR, (DMSO): resolved protons δ 11.2 (s, 1H, thymine aromatic), 8.7 (d, 1H, J=8.8 Hz, Thymine-NH-) 7.8-7.3 (m, 8H, Florenyl aromatic protons), 5.6 (d, 1H, J=8.8 Hz), 5.37 (dd, 1H, J=10.2, 3.8 Hz), 5.15 (d, 1H, J=3.3 Hz), 5 (t, 1H, J=10 Hz), 4.6 (m, 2H), 4.3 (d, 1H, J=6 Hz), 4.2 (m, 2H), 4 (d, 1H, J=11 Hz, 2.2-2 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ($CDCl_3$ ^{13}C-NMR ($CDCl_3$): δ 170.13, 169.62, 143.91, 140.76, 127.67, 127.13, 125.17, 120.15, 108.05, 72.60, 70.88, 65.58, 47.84, 46.75, 33.39, 24.53, 21.03, 20.61, (sugar-CO-$\underline{C}H_3$ groups), 11.99 (Thymine-CH_3).

HRMS $(M+H)^+$, calcd (found) for $C_{42}H_{48}N_5O_{17}$ is 894.3045 (893.3065).

EXAMPLE 48

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4-tri-*O*-acetyl fucose-1-yl)-amide]-*OH* (11s)

Preparation: procedure (f). Yield = 88%.

Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) 836 *m/z* (M+H); 7.8-7.3 (m, 8H, Florenyl aromatic protons), 7.2 (s, 1H, Thymine-NH-), 5.3 (overlapping s, 2H), 5.2 (d, 1H, J=3 Hz), 4.66 (s, 1H), 4.4 (m, 2H), 4.25 (m, 1H), 4 (m, 1H), 3.5 (m, 3H), 3.15 (m, 2H), 2.2-2 (singles, 9H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3), 1.1 (s, 3H, fucose-CH_3); ^{13}C-NMR (CD_3OD): δ 172.30, 171.81, 170.68, 170.30, 169.96, 167.74, 165.39, 157.35, 151.41, 143.84, 143.74, 142.15, 141.04, 134.35, 132.27, 131.60, 131.49, 128.52, 128.40, 127.30, 126.68, 124.77,

124.07, 119.44, 109.36, 86.67, 77.61, 71.92, 71.46, 71.33, 70.51, 68.57, 68.26, 68.12, 67.93, 66.40, 58.96, 39.00, 35.92, 33.26, 25.26, 24.57, 19.27, 19.11, 19.05, 15.05, 10.90.
HRMS $(M+H)^+$, calcd (found) for $C_{40}H_{46}N_5O_{15}$ is 836.2990 (836.2980).

EXAMPLE 49

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-acetyl glucosamine-1-yl)-amide]-*OH* (12s)

Preparation: procedure (f). Yield = 90%.
Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 893 (M+H); ^{1}H-NMR, (CD_3OD): δ 7.8-7.3 (m, 8H, Florenyl aromatic protons), 7.2 (d, 1H, J=9Hz, Thymine-NH-), 5.3 (m, 2H), 5.1 (d, 1H, J=9.7Hz), 4.7 (m, 1H), 4.4 (m, 2H), 4.2 (m, 2H), 4.1 (m, 1H), 3.9 (m, 1H), 3.6-2.8 (multiplets, 5H), 2.1-1.9 (4s, 12H, sugar acetyl protons), 1.8 (s, 3H, Thymine-CH_3); ^{13}C-NMR (CD_3OD): δ 173.76, 172.94, 172.43, 172.05, 171.40, 170.14, 169.26, 166.94, 158.85, 153.13, 152.87, 145.32, 143.72, 142.59, 130.13, 129.93, 128.88, 128.26, 126.24, 121.05, 111.17, 110.92, 79.53, 74.85, 74.62, 69.97, 69.82, 67.86, 63.34, 59.82, 54.28, 40.46, 37.16, 23.09, 23.01, 22.87, 22.74, 20.72, 12.39.
HRMS $(M+H)^+$, calcd (found) for $C_{42}H_{49}N_5O_{16}$ is 893.3205 (893.3232).

EXAMPLE 50

Fmoc-*N*-(Thymine-1-ylacetyl)Asp-[O-(2,3,4,5-tetra-acetyl galactosamine-1-yl)-amide]-*OH* (13s)

Preparation: procedure (f). Yield = 91%.
Mp = ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 893 (M+H); ^{1}H-NMR, (CD_3OD): δ 7.8-7.3 (m, 8H, Florenyl aromatic protons), 7.2 (s, 1H, Thymine-NH-), 5.4 (s, 1H), 5.3 (d, 1H, J=9.5 Hz), 5.2 (dd, 1H, J=11, 3.3 Hz), 5.1 (m, 1H), 4.7 (s, 1H), 4.4 (m, 2H), 4.3-4.1 (m, 4H), 3.8 (m, 1H), 3.6 (m, 1H), 3.5-2.8 (multiplets, 5H), 2.2-1.9 (4s, 12H, sugar acetyl protons), 1.85 (s, 3H, Thymine-CH_3); ^{13}C-NMR (CD_3OD): δ 174.06, 173.57, 172.94, 172.18, 172.05, 171.81, 171.74, 169.28, 166.98, 158.88, 153.14, 152.9, 145.34, 143.75, 142.62, 135.10, 134.97, 133.05, 131.43, 130.22, 129.95, 128.87, 128.24, 126.24, 121.03, 110.89, 80.06, 73.36, 72.71, 68.91, 68.23, 67.89, 62.86, 59.86, 40.46, 37.19, 26.55, 23.12, 20.70, 12.39.
HRMS $(M+H)^+$, calcd (found) for $C_{42}H_{49}N_6O_{16}$ is 893.3205 (893.3245).

EXAMPLE 51

4-C-(2,3,4,6-tera-O-acetyl-galactose-1-yl)-2[N,N(2-fmoc-aminoethyl)-(thymine-1-yl-methyl-carbonyl)-aminobutanoic acid (14s)

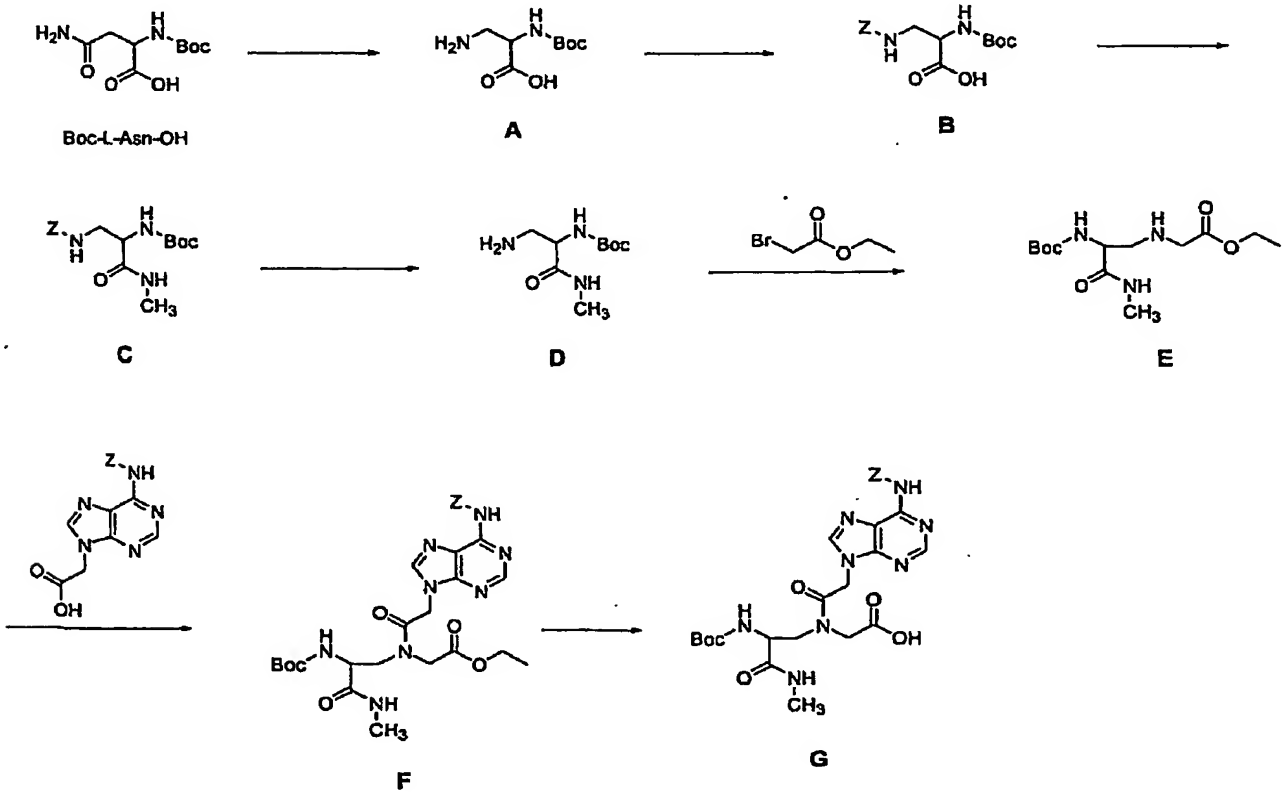
920 mg (1 mmol) **44** was added to 10 ml solution of 5% triethylsilane in trifluoroacetic acid at 0°C and stirred until TLC did not show any starting material left. 50 ml DCM was added and volatile removed under vacuum. Further 3 x 100 ml DCM was added and evaporated in order to removal of TFA. The product was precipitated with adding diethylether. 830 mg (0.94 mmol) titled compound was obtained as white powder (Yield = 94%).

Mp= ; $[\alpha]_D^{22}$= (*c*=0.5, methanol); MS (FAB) *m/z* 865 (M+H); ^{1}H-NMR, (CD_3OH): δ 7.8-7.3 (m, 8H, fmoc aromatic), 7.2 (s, 1H, thymine-NH-), 5.4 (overlapping s, 2H), 5.3 (m, 1H), 4.7(s, 1H), 4.6 (m, 1H), 4.5(d, 2H, J=6.6 Hz), 4.2 (overlapping s, 2H), 4.1 (overlapping s, 2H), 3.6 (s, 1H), 3.5 (overlapping s, 2H), 3.3 (s, 1H), 2.2-2 (4s, 12H, sugar acetyl protons), 1.85 (s, 3H, thymine-methyl), ^{13}C-NMR (CD_3OD): δ 172.75, 171.22, 170.86, 170.75, 170.63, 170.52, 168.56, 165.80, 157.63, 151.63, 144.09, 142.89, 142.70, 141.43, 127.66, 127.01, 125.00, 119.82, 109.43, 72.16, 68.62, 68.45, 68.26, 68.08, 39.52, 33.60, 31.59, 25.58, 24.91, 24.76, 22.55, 21.73, 19.60, 19.43, 13.31, 11.16.

HRMS $(M+H)^+$, calcd (found) for $C_{42}H_{49}N_4O_{16}$ is 865.3140 (865.3144).

EXAMPLE 52

Solid Phase Synthesis of Type IV PNA monomers



N^{α}-Boc-Diaminopropionic acid

A) To a solution of Boc-L-Asn-OH (15.0 g, 60.3 mmol) in EtOAc (75 mL), CH_3CN (75 mL) and water (30 mL) at 10°C was added PIDA (24.9 g, 77.3 mmol, 1.3 eq.). The mixture was stirred for 30 min, heated to 20□C and stirred for further 2.5 h. The mixture was heated to 70°C until completely dissolved and then slowly cooled to 20□C and filtered. The remanence was washed with EtOAc (2 x 50 mL) and dried. Yield 8.9 g (68%). ^{1}H NMR (DMSO-d_6 + TFA) δ 8.06 (bs, 3NH), 7.36 (d, 1NH, J = 8.7 Hz), 4.40-4.25 (m, 1H), 3.35-3.25 (m, 1H), 3.15-3.00 (m, 1H), 1.51 (s, 9H). MS: $[M+H]^+$: expected: 205.1; observed: 205.1.

N^{α}-Boc-N^{β}-Z-Diaminopropionic acid

B) To a solution of N^{α}-Boc-Diaminopropionic acid (8.90 g, 43.6 mmol) in water (270 ml) was added $NaHCO_3$ (7.5 g) and subsequently a solution of benzyl chloroformate (6.85 mL, 48.0 mmol, 1.1 eq.) in Et_2O (30 mL) was added dropwise with vigorous stirring. Another quantity of $NaHCO_3$ (7.5 g) was added, and the mixture was stirred vigorously for 3 h. The mixture was washed with Et_2O (2 x 200 mL), cooled to 0□C, acidified with solid citric acid to pH 3 and extracted with EtOAc (2 x 200 mL). The combined organic phases were washed with 10% aq. citric acid (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a foam. Yield 12.55 g (85%). ^{1}H NMR (acetone-d_6) δ 11.22 (bs, 1H), 7.40-7.20 (m, 5H), 6.58 (bs, 1NH), 6.23 (d, 1NH, J = 7.7 Hz), 5.07 (s, 2H), 4.35-4.25 (m, 1H), 3.65-3.60 (m, 1H), 3.55-3.50 (m, 1H), 1.39 (s, 9H). ^{13}C-NMR (acetone-d_6) δ 171.76, 157.22, 155.89, 137.70, 128.69, 128.11, 78.91, 66.22, 54.56, 42.57, 28.03. MS: expected: 338.4; observed: 338.2.

(2-tert-Butoxycarbonylamino-2-methylcarbamoyl-ethyl)-carbamic acid benzyl ester

C) To a solution of N^{α}-Boc-N^{β}-Z-Diaminopropionic acid (11.5 g; 34 mmol), HOBt (7,8 g, 51 mmol, 1,5 eq.) and methylamine (8M in ethanol, 6.4 mL, 1.5 eq.) in DCM:DMF (10:1; 110 mL) at 0°C was added DCC (8.4 g, 40.8 mmol, 1.2 eq.) and the mixture was stirred for 2 h while warming to 20°C. 10% aq. $NaHCO_3$ (30 mL) was added and the mixture was stirred for further 30 min. The mixture was filtered and the phases separated. The organic phase was extracted with aq. $KHSO_4$ (0.5M, 30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a white solid. Yield 7.5 g (63%). MS: [M+H] expected: 352.4; observed: 351.9.

(2-Amino-1-methylcarbamoyl-ethyl)-carbamic acid tert-butyl ester

D) To a solution of (2-tert-Butoxycarbonylamino-2-methylcarbamoyl-ethyl)-carbamic acid benzyl ester (7.0 g, 19.9 mmol) in methanol (100 mL) was added Pd/C (310 mg). The mix-

ture was hydrogenated for 1 h at 1 atm, filtered (celite) and concentrated *in vacuo* to a foam. Yield 4.3 g (100%). MS: [M+H] expected: 218.30; observed: 218.07.

(2-tert-Butoxycarbonylamino-2-methylcarbamoyl-ethylamino)-acetic acid ethyl ester

E) To a stirred mixture of (2-Amino-1-methylcarbamoyl-ethyl)-carbamic acid tert-butyl ester (4.2 g, 19.4 mmol) and triethylamine (3.5 mL, 25.2 mmol, 1.3 eq.) in THF (80 mL) was added a solution of ethyl bromoacetate (2.37 mL, 21.3 mmol, 1.1 eq.) in THF (20 mL) dropwise over 15 min. The mixture was stirred for 16 h, filtered and concentrated *in vacuo* to an oil, which was purified by flash chromatography (silica, 7.5% methanol in dichloromethane). Yield: 3.5 g (59%). MS: [M+H] expected: 304.36; observed: 304.04.

[[2-(6-Benzyloxycarbonylamino-purin-9-yl)-acetyl]-(2-tert-butoxycarbonylamino-2-methylcarbamoyl-ethyl)-amino]-acetic acid ethyl ester

F) To a stirred suspension of (2-tert-Butoxycarbonylamino-2-methylcarbamoyl-ethylamino)-acetic acid ethyl ester (3.27 g, 10 mmol) and DHBt-OH (1.2 eq.) in DMF (50 mL) was added a solution of (6-benzyloxy-carbonylamino-purin-9-yl)-acetic acid (3.0 g, 10 mmol, 1.0 eq.) in DMF (25 mL). The mixture was cooled to 0°C and DCC (2.26 g, 11 mmol, 1.1 eq.) was added. The mixture was stirred for 1 h at 0°C and then at 20°C for 16 h. DCU was removed by filtration and washed with DMF (20 mL). The filtrate was concentrated in vacuo to 25% volume and DCM (100 mL) was added. The solution was washed with 0.5M $KHSO_4$ (2 x 50 mL) and 5% aq. $NaHCO_3$ (2 x 50 mL) and activated carbon (1 g) was added. The mixture was stirred for 1 h, filtered and concentrated in vacuo to an oil, which was purified by flash chromatography (silica, 5% methanol in dichloromethane). Yield: 2.7 g (44%) MS: [M+H] expected: 613.27; observed: 613.10.

[[2-(6-Benzyloxycarbonylamino-purin-9-yl)-acetyl]-(2-tert-butoxycarbonylamino-2-methylcarbamoyl-ethyl)-amino]-acetic acid

G) To a mixture of [[2-(6-Benzyloxycarbonylamino-purin-9-yl)-acetyl]-(2-tert-butoxycarbonylamino-2-methylcarbamoyl-ethyl)-amino]-acetic acid ethyl ester (2.6 g, 4.25 mmol) in THF (50 mL) was added a mixture of LiOH (1.25 eq.) in water (7 mL). The mixture was stirred for 2 h and then concentrated in vacuo to 15% vol. pH was adjusted to ~2.5 with 1M aq. HCl and ethyl acetate (20 mL) was added. The phases were separated and the organic phase was concentrated in vacuo to a foam. Yield: 2.47 g (99%). MS: [M+H] expected: 585.23; observed: 585.3.

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20. Litt. 3
21. Litt.4
22. Litt. 7
23. Litt. 8
24. Litt. 9
25. Litt. 10
26. Litt. 11

27. Litt. 12
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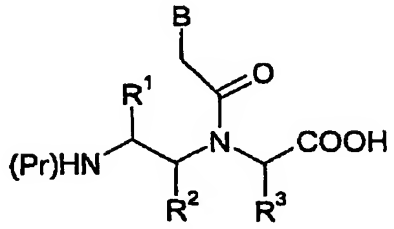
CLAIMS

1. A modified Peptide Nucleic Acid (PNA) monomer of formula (I):

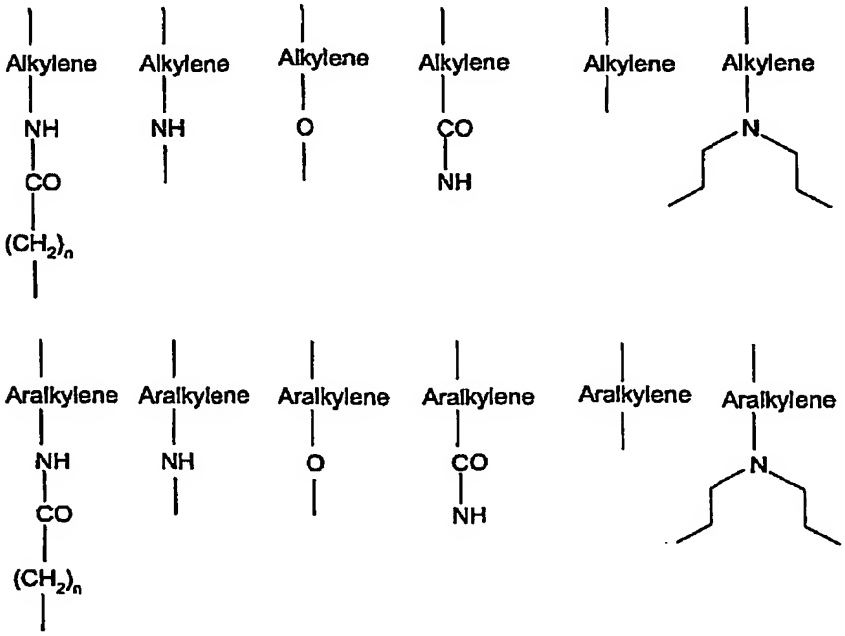


(I)

wherein B is a naturally-occurring nucleobase preferably A, T, G, or C, or a non-naturally-occurring nucleobase;

(Pr) is hydrogen or a protection group;

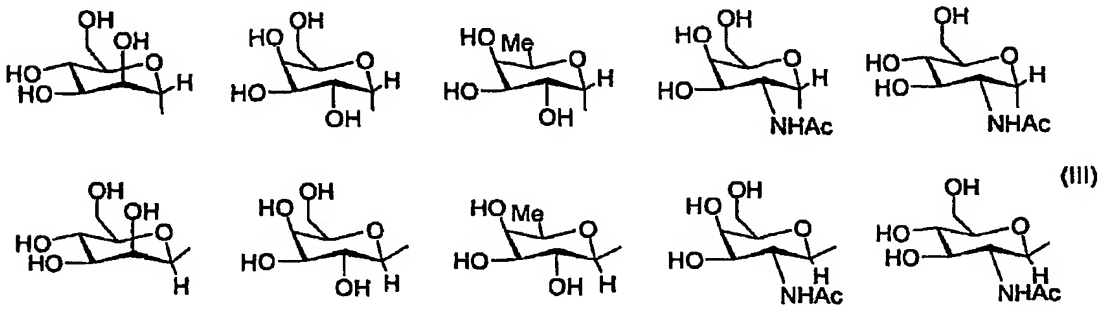
R^1, R^2 and R^3 are, independently, hydrogen, an amino acid side chain, or an C_{2-6}-alkyl, aryl, aralkyl, heteroaryl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy- or alkoxy- or alkylthio-substituted C_{1-6}-alkyl, $-NR^4R^5$, (wherein R^4 and R^5 independently are hydrogen, C_{1-6}-alkyl, hydroxy- or alkoxy- or alkylthio-substituted C_{1-6}-alkyl), or Z^1-Z^2, wherein Z^1 is a bond or one of the radicals of formula (II):



(II)

wherein n is form 0 to 8;

and Z^2 is alfa- or beta forms of a monosaccharide, a disaccharide, a polysaccharide, or one of the radicals of formula (III):

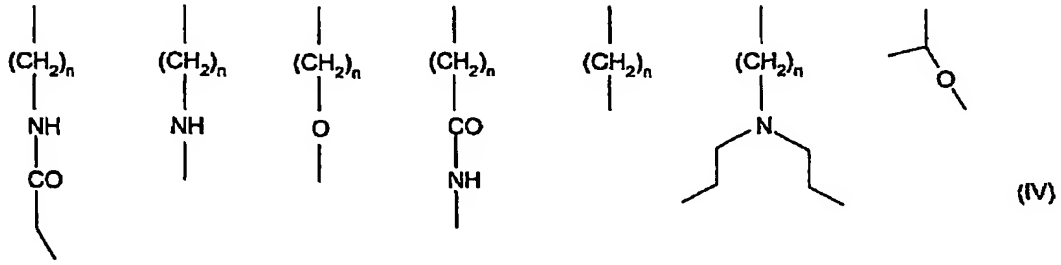


(III)

provided that at least one of R^1, R^2, or R^3 is Z^1-Z^2.

2. A compound according to claim 1, wherein the amino acid side chain is selected from the group consisting of C_{1-6}-alkyl, 3-guanidinopropyl, carboxymethyl, aminocarboxymethyl, mercaptomethyl, 2-carboxyethyl, aminocarboxyethyl, imidazol-4-yl-methyl, 4-aminobutyl, 2-(methylthio)ethyl, benzyl, hydroxymethyl, 1-hydroxyethyl, 3-indolyl, 4-hydroxybenzyl, 2-hydroxymethyl, or 3-ureidopropyl, 4-pyridomethyl (or 1-methylpropyl, 2-methylpropyl or 1-methylethyl).

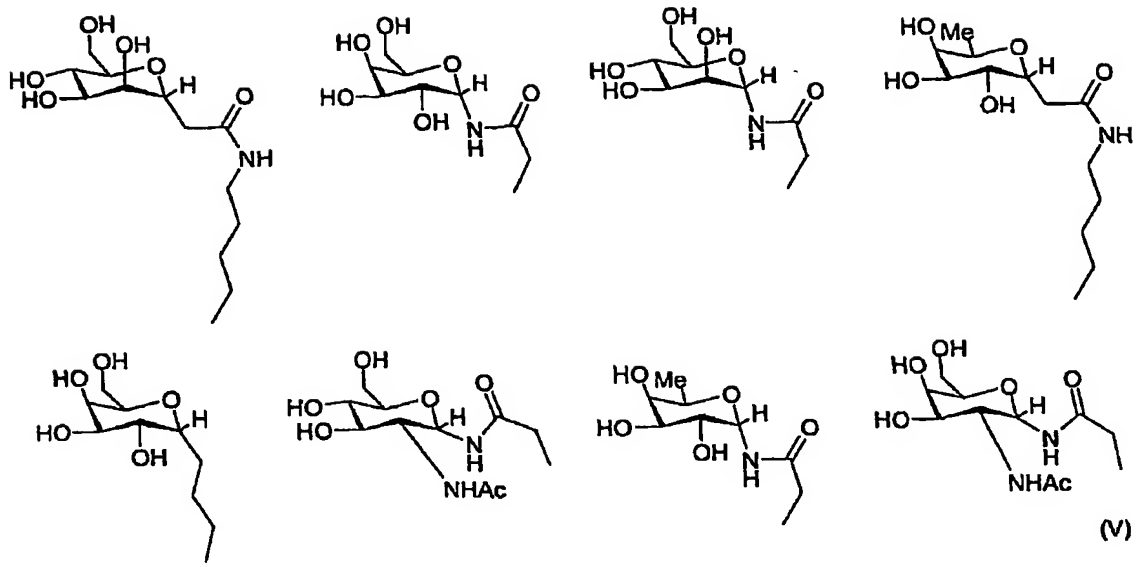
3. A compound according to claim 1 or 2, wherein Z^1 is one of the radicals of formula (IV):



(IV)

4. A compound according to claim 1, wherein the disaccharide is selected from the group consisting of alfa and beta forms of sucrose, lactose, and maltose.

5. A compound according to claim 1 or 3, wherein Z^1-Z^2 comprises ligands of formula (V):



(V)

or beta-forms hereof.

6. A peptide nucleic acid oligomer with from 4 to 50 monomers selected from the group consisting of PNA monomers and at least one monomer of claim 1 to 5.

7. A peptide nucleic acid molecule comprising a peptide nucleic acid oligomer of claim 6 and a conjugate bound to said peptide nucleic acid either directly or through a linking moiety, wherein said conjugate is a reporter enzyme, a reporter molecule, a steroid, a carbohydrate, a terpene, a peptide, a protein, an aromatic lipophilic molecule, a non aromatic lipophilic molecule, a phosphorlipid, an intercalator, a cell receptor binding molecule, a crosslinking agent, a water soluble vitamin, a lipid soluble vitamin, an RNA/DNA cleaving complex, a metal chelator, a porphyrin, an alkylator, or a polymeric compound selected from polymeric amines, polymeric glycols and polyethers.

8. Use of a PNA compound according to any of claims 1 to 7 in the manufacture of a medicament for the treatment or prevention of bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune and immunological disorders, or for disinfecting non-living objects, such as surgery tools, hospital inventory, dental tools, slaughterhouse inventory and tool, dairy inventory and tools, barbers and beauticians tools, and the like.

9. Use of a PNA compound according to any of claims 1 to 7 in the manufacture of a composition for the treatment or prevention of bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune and immunological disorders, or for disinfecting non-living objects, such as surgery tools, hospital inventory, dental tools, slaughterhouse inventory and tool, dairy inventory and tools, barbers and beauticians tools, and the like.

10. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims 1 to 7 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

11. A composition according to claim 11 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any one of the preceding compound claims 1-7 or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition according to any one of the claims 10 to 11 for oral, nasal, transdermal, pulmonal, or parenteral administration.

13. A pharmaceutical composition according to claim 10 to 12 for the treatment or prevention of bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune and immunological disorders, or treatment of non-living objects, the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims 1 to 8 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

14. A method of treating a disease selected from bacterial, viral, protozoal, and fungal infections, cancer, metabolic diseases, cardiovascular diseases, autoimmune or immunological disorders comprising administering to a patient in need thereof an efficient amount of a compound of claim 1 to 7, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims 1-7 or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

15. The method according to claim 14, wherein the effective amount of the compound ac-

cording to any one of the preceding compound claims 1 to 7 or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.

ABSTRACT

The present invention concerns novel drugs for use in combating various diseases. More particular the invention concerns peptide nucleic acid (PNA) drugs, which are optionally modified in order to obtain novel PNA molecules with cell-specific delivery.